Alzheimer's Disease Through the Symbiont Lens:

Candida albicans, Amyloid as Defensive Encapsulation, and the SOX9-MEGF10-Hk1 Astrocyte Triad

A Stuck-State Manifestation Within the Redacted Science Framework

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Abstract

Anti-amyloid antibody therapy for Alzheimer's disease has produced reliable biomarker engagement (PET-detectable amyloid clearance) without functional benefit. Across more than seventeen trials encompassing over twenty thousand participants, the absolute cognitive effects have been characterized as absent or trivial, with no measurable benefit in women or in APOE4 carriers (60 to 75 percent of patients). In parallel with this twelve-year program, a separate published literature has accumulated documenting fungal presence in one hundred percent of Alzheimer's brain tissue sampled across multiple regions, antimicrobial peptide function of amyloid β against *Candida albicans* and other pathogens, causal demonstration of fungal-induced amyloid deposition in mouse and human iPSC-organoid models, and convergent return of antifungal compounds as top-ranked hits from blind drug screens against amyloid β aggregation across two independent screening methodologies.

This paper integrates the published record into a coherent disease architecture. Alzheimer's disease is reframed as the brain-stage manifestation of chronic *Candida albicans* dysregulation, with amyloid plaques functioning as antimicrobial defensive encapsulation around live fungal targets. The host's astrocytic SOX9-MEGF10 phagocytic clearance machinery is documented to fail through autoantibody-mediated functional decoupling in chronic-*Candida* exposure, while the parallel SOX9-Hk1-lactate-H3K9 lactylation inflammatory pathway remains operational, producing the chronic locked-in inflammatory state of symptomatic disease.

The reframe accounts for anti-amyloid antibody trial failures, the ARIA adverse event class as encapsulation-stripping signature, and the differential failure across patient subpopulations. The therapeutic prediction is that antifungal therapy targeting *Candida albicans* in early-stage Alzheimer's disease with documented fungal burden will produce cognitive benefit substantially exceeding approved anti-amyloid antibodies. A multi-arm adaptive platform trial design is specified.

The integration positions Alzheimer's disease within the Redacted Science Research Initiative's stuck-state framework as the terminal manifestation of the lifetime symbiont dysregulation visible in earlier-life conditions including type 2 diabetes, irritable bowel syndrome, and Parkinson's disease.

Keywords: Alzheimer's disease; *Candida albicans*; amyloid β; antimicrobial encapsulation; SOX9; MEGF10; astrocyte; antifungal therapy; stuck-state framework; Redacted Science Research Initiative; #TheArchitect

§I. Introduction

Alzheimer's disease has been the most heavily funded research target in modern neurology for over four decades, with cumulative investment in amyloid-targeted therapeutics estimated above $30 billion. The amyloid hypothesis has shaped clinical trials, drug development pipelines, and biomarker frameworks. Three monoclonal antibodies (aducanumab, lecanemab, donanemab) received FDA approval based on demonstrated amyloid clearance from positron emission tomography. None has produced more than marginal cognitive benefit. The lecanemab Clarity AD trial reported a 0.45-point difference on the Clinical Dementia Rating Sum of Boxes over 18 months, an effect size below the minimum observable change on the scale used (van Dyck et al. 2023). The DIAN-TU trial demonstrated amyloid clearance with gantenerumab over 4 to 7 years of treatment in dominantly inherited AD, with no cognitive benefit (Salloway et al. 2021). A 2026 evidence review of 17 trials encompassing more than 20,000 participants concluded that the absolute effects of anti-amyloid drugs on cognitive decline were "absent or trivial" (Nonino et al. 2026). Treatment showed no benefit at all in women and in APOE4 carriers, a population that comprises 60 to 75 percent of AD patients (Imbimbo et al. 2024; van Dyck et al. 2023 supplementary analyses).

> [*The amyloid hypothesis predicts that removing the proximate cause of pathology should restore function. The clinical record demonstrates the opposite: removing the proxy does not change the disease, and in the patient subgroups that constitute the majority of cases, treatment produces no measurable benefit. This pattern is what the framework would expect if the proxy is not the cause.*]

In parallel with the anti-amyloid program, a separate research literature has accumulated since 2014. Alonso, Pisa, and colleagues at the Centro de Biología Molecular Severo Ochoa demonstrated detectable fungal infection in brain tissue from Alzheimer's patients across multiple regions (frontal cortex, cerebellum, entorhinal cortex/hippocampus, choroid plexus), with fungal cells and hyphae visualized by immunohistochemistry against five different fungal antibodies, and absent from controls (Pisa et al. 2015). Companion work demonstrated that 28 of 29 AD patients tested positive for systemic disseminated fungal polysaccharides on Fungitell assay (Alonso et al. 2014). Wu, Corry, and colleagues at Baylor College of Medicine demonstrated that *Candida albicans* introduced via the bloodstream in mice crosses the blood-brain barrier, forms characteristic granulomatous structures around yeast aggregates, and induces local accumulation of amyloid precursor protein and cleaved amyloid β peptides through fungal aspartyl proteinase activity (Wu et al. 2019; Wu et al. 2023). Blind drug screens against amyloid β aggregation, conducted by independent research groups using different methodological approaches, have repeatedly returned antifungal compounds as their highest-ranked hits (Kumari et al. 2021; Xie et al. 2024). Mechanistic work on the astrocytic compartment has identified a transcription factor program governing both amyloid clearance through MEGF10-mediated phagocytosis and inflammatory amplification through hexokinase-1 driven glycolytic lactate production and histone lactylation, with documented genetic and immune mechanisms that

decouple transcript expression from functional output in chronic disease (Choi et al. 2025; Chen et al. 2025; Hedstrand et al. 2001).

These findings are not obscure. They appear in *Scientific Reports*, *Nature Communications*, *Cell Reports*, *Nature Neuroscience*, and *Journal of Alzheimer's Disease*. They have accumulated across three continents over more than a decade. They have not been integrated into the dominant clinical framework for Alzheimer's disease. No major Phase III trial of antifungal therapy in AD has been registered, despite explicit calls for such trials from the original investigators in 2014 and 2015.

The present paper performs that integration. The argument advanced is that Alzheimer's disease, as conventionally defined, is the brain-stage manifestation of a chronic dysregulation in the host's relationship with *Candida albicans*. The organism originates as a gastrointestinal commensal in approximately half of healthy adults, transitions under decades of selection pressure (dietary substrate, antibiotic exposure, immune drift) from luminal yeast to tissue-invasive hyphal form, translocates across the gastrointestinal barrier and across the blood-brain barrier, establishes localized brain infection that the host encapsulates with amyloid β as antimicrobial defense, and over time produces a failure mode in the astrocytic SOX9-MEGF10-Hk1 architecture that converts the encapsulation system into a chronic inflammatory state. The amyloid plaques characteristic of AD are reframed within this argument as defensive encapsulation around live fungal targets, with their removal explaining both the biomarker success and the functional failure of current anti-amyloid therapeutics. The therapeutic implication, supported by the convergent drug-screen data and by buried positive trial results from 2004 (Loeb et al. 2004), is that antifungal therapy should be tested as a disease-modifying intervention.

The argument is positioned within the Redacted Science Research Initiative, an integrative framework treating *C. albicans* as a coevolved biochemical computer producing a physiologically distinct human phenotype designated *Homo candidus*. The framework's foundational papers (Craddock: Paper A: Biochemical Computer, Paper B: Saline Oscillation Hypothesis, Pan-Mammalian Hypothesis,) establish the organism as a symbiont, regulator, and metabolic coprocessor rather than an opportunistic invader. The Stuck-State series (Craddock Stuck State) describes specific disease entities (T2D, Obesity, Anorexia, IBS, Parkinson's, Endometriosis) as failure modes of the host-symbiont relationship: organism-mediated programs that fail to receive their exit signal and lock into chronic dysfunction. The Endocrine Interface paper (Craddock, Pituitary and Thyroid) extends this architecture into the pituitary and thyroid axes. The Implications paper (Craddock, Implications) develops the systemic consequences of recognizing the framework. The Terminal Onset Diabetes Insipidus case series (Craddock, Case Studies) supplies the longitudinal phenotype data underlying the framework. AD, in the framework's reading, sits at the terminal end of the same lifetime arc, the brain-stage manifestation of the same symbiont dysregulation visible in T2D and IBS earlier in life.

[*The Redacted Science framework is distinctive in that it generates testable predictions across disease boundaries from a single mechanistic claim. Conventional AD frameworks generate predictions only within AD itself. The framework's claim that AD is the brain-stage manifestation of a lifetime arc predicts cross-disease comorbidity patterns, age-dependent disease ordering, and therapeutic responses to antifungal intervention that the conventional framework cannot generate. The empirical content of this paper is that those predictions are already supported by published data the field has not integrated.*]

The remainder of this paper proceeds as follows. §II describes the gut origin of *C. albicans* colonization and its dietary and pharmacological substrates. §III traces translocation from gut to systemic circulation and to brain. §IV documents brain colonization across human postmortem and animal model literature. §V develops the reframe of amyloid β as antimicrobial defensive encapsulation and addresses the empirical capstone of anti-amyloid trial failures. §VI examines the astrocytic SOX9-MEGF10-Hk1 architecture and its failure mode. §VII summarizes the convergent therapeutic literature. §VIII presents testable predictions; §IX presents biomarker stratification implications; §X documents the institutional pattern that has prevented integration. §XI concludes.

§II. Gut Origin: The Reservoir

Candida albicans is a commensal yeast in the gastrointestinal tract of approximately 50 percent of healthy adults, with the oral cavity, esophagus, lower bowel, and vaginal tract serving as the primary reservoirs. The organism's residence in the gut is bidirectional with host metabolism: it depends on luminal substrate for proliferation, and it modulates host immune signaling, barrier function, and metabolic state through cell-wall β-glucan presentation, secreted aspartyl proteinases, candidalysin, and a range of metabolite outputs. The framework treats this baseline state as the symbiont relationship in its functional configuration (Craddock: Biochemical Computer, Pan-Mammalian), with chronic disease emerging when the relationship transitions from luminal commensal coexistence to tissue-invasive dysregulation.

Two classes of long-acting selection pressure operate continuously across a lifetime to shape this transition: dietary substrate composition and pharmacological exposure to antibiotics.

Dietary substrate determines the organism's growth rate and metabolic configuration. *C. albicans* is heavily glucose-favoring; its sugar sensor Gpr1, which has been documented as a coevolved metabolic input channel reading host immune-stress lactate output (treated in detail in Paper B), evolved from a sugar-sensing architecture that the organism retained for both substrates simultaneously. Modern Western dietary patterns characterized by elevated refined carbohydrate intake provide chronic glucose substrate that supports luminal expansion. Dietary intervention data corroborates the substrate dependency: a modified Mediterranean ketogenic diet administered to subjects with mild cognitive impairment shifted both gut mycobiome

composition and cerebrospinal fluid AD markers including amyloid β and tau within months (Nagpal et al. 2020). The intervention demonstrates a causal chain rather than correlation: changing the substrate available to the organism changes the organism's representation in the gut, and that change tracks with measurable shifts in central nervous system markers of the disease.

[*The Nagpal intervention is what the framework's prediction structure looks like operationalized. Diet is not acting on AD pathology directly. Diet is acting on the organism's metabolic substrate, the organism's representation in the gut shifts, and AD markers move because the disease is a downstream consequence of organism dysregulation. The conventional dietary AD literature treats the cognitive effect as direct; the framework treats it as mediated.*]

Antibiotic exposure operates orthogonally. Broad-spectrum antibacterial therapy suppresses the bacterial competitors that constrain *C. albicans* expansion in the lumen without affecting the fungus directly. Post-antibiotic candidiasis is a recognized clinical entity, and the cumulative effect of repeated antibiotic courses across a lifetime represents a continuous selection pressure favoring the symbiont relative to its bacterial environment. The mouse-model literature documents this dependency directly: stable *C. albicans* colonization of the murine gut typically requires antibiotic-induced dysbiosis to establish, and the antibiotic regimen functions as a tractable proxy for the chronic competitive disruption produced by repeated human antibiotic exposure (Cornitius 2025, UTSA dissertation; Vautier et al. 2012).

The framework predicts that lifetime cumulative antibiotic exposure should track with AD risk in a dose-dependent fashion, controlling for the underlying conditions that prompted antibiotic prescription. The dose-response association has been documented at population scale (Kim et al. 2022) with caveats and integration with fungal burden markers treated in detail in §VIII.4.

[*Lifetime antibiotic exposure is one of the most thoroughly documented variables in modern clinical practice. Every prescription is captured. Kim et al. (2022), analyzing 313,161 participants in the South Korean National Health Insurance Service-Health Screening Cohort, reported that 91 or more cumulative antibiotic prescription days produced a 1.46-fold adjusted hazard ratio for AD specifically (95% CI 1.17 to 1.81), with a dose-response gradient across the exposure range. The empirical observation is now in the published record; the framework's distinctive contribution is the mechanism through Candida-favoring selection pressure, which connects this finding to the rest of the architecture and is treated in §VIII.4.*]

The gut mycobiome composition in AD patients shows a pattern that initially appears to weaken the framework's case but on closer reading strengthens it. Ling and colleagues (Ling et al. 2021), in a study of 88 Chinese AD patients and 65 age-matched cognitively normal controls, found altered taxonomic composition of fecal fungal microbiota in AD patients with enrichment of *Candida tropicalis* and *Schizophyllum commune* and depletion of *Rhodotorula mucilaginosa*.

The expected finding, given the framework's prediction of *C. albicans* as central organism, would have been *C. albicans* enrichment in AD patient feces. The observed finding is that *C. albicans* is not the dominant signal in AD patient feces, and *C. tropicalis* (the secondary occupant) correlates with elevated TNF-α and IP-10 inflammatory markers.

The conventional reading of this finding is that *C. albicans* is not specifically implicated in AD. The framework reads it differently. Stool sequencing detects what is shed into the lumen. Tissue-resident hyphal *C. albicans* does not shed efficiently. The framework's prediction of the symbiont's transition from luminal commensal yeast to tissue-invasive hyphal form predicts exactly what Ling observes: *C. albicans* present in tissue (vasculature, mucosa, and ultimately brain, as documented in §IV) but underrepresented in feces, with the luminal niche reorganized around secondary fungal occupants. The community reorganization, with *C. tropicalis* taking the niche left by *C. albicans* migration and producing the inflammatory signal Ling detected, is the gut-side signature of a symbiont relationship that has transitioned out of the lumen.

> [*The Ling pattern is what a framework-correct prediction looks like when the conventional reading interprets it as falsification. The organism's location is not where the older framework expected it. The organism's location is where the new framework predicted it. Distinguishing these two conditions requires sampling the right compartment.*]

The capsaicin-population data provides an inverse natural experiment. Populations with chronic dietary capsaicin exposure (Mexican, Indian, Sichuan, Thai) show measurably lower stature and longer lifespans relative to comparable populations on lower-capsaicin diets. The mechanistic basis was clarified by Wang and colleagues (Wang et al. 2025), who demonstrated in rats that capsaicin-rich diet recapitulates idiopathic short stature through gut inflammation, exosomal miR-17-3p elevation, and downstream suppression of chondrocyte growth signaling, with growth hormone and IGF-1 levels remaining normal. Within the capsaicin-population epidemiology, this mechanism explains the stature effect. It does not explain the longevity effect. Conventional growth-axis hormones associated with longevity (specifically reduced IGF-1) are not modulated. The longevity benefit must be mediated by a variable other than the conventional endocrine growth axis.

Capsaicin is a documented antifungal agent against *C. albicans*, with established membrane-disruption activity at concentrations achievable through dietary exposure. The framework's reading of the capsaicin-population pattern is that chronic dietary antifungal pressure suppresses the organism across decades, producing both reduced stature (via the Wang mechanism) and reduced terminal-stage symbiont colonization (extending lifespan). The gut-mediated component of this reading is corroborated by Li et al. (2026), who demonstrated that capsaicin's amelioration of AD-like pathology in mice operates through gut microbiota-dependent 24-hydroxycholesterol metabolism, independent of TRPV1 signaling. The TRPV1-independence rules out the direct pain-pathway explanation for the AD-protective effect; the gut-microbiota dependency is consistent with the framework's reading that capsaicin's effect on AD

trajectory operates through host-symbiont modulation rather than central neural pathways. The reduction in symbiont burden has metabolic costs, including the disease patterns documented in the same populations (high T2D rates in Mexico, expanding T2D in India). Within the framework, these patterns reflect chronic disruption of the symbiont relationship rather than its absence: dysfunction without progression to the terminal pituitary-colonization endgame, producing morbidity without the symbiont-driven mortality. Disease without death.

> [*Capsaicin populations are a population-scale natural experiment in chronic suppressed-symbiont phenotype. The framework predicts altered AD trajectory in these populations specifically: delayed terminal but possibly preserved cognitive curves, distinct from the trajectory observed in low-capsaicin populations. The epidemiological data exists. The analysis has not been performed.*]

Two further inputs to gut origin warrant brief mention. First, the gut-residence baseline is not symmetric across host populations: vaginal and oral *C. albicans* reservoirs cycle differently across reproductive years in women versus men, and hormonal modulation of mucosal immunity creates sex-specific reservoir dynamics that may explain the sex-asymmetric AD incidence and the documented failure of lecanemab to produce benefit in women (van Dyck et al. 2023). Second, oral *Candida* provides an additional reservoir whose burden is not captured by stool sampling. The oral health and oral mycobiome literature has produced direct empirical findings consistent with the framework's reading. Aragón et al. (2018) documented poorer oral health in AD patients in a multicenter case-control study. Cestari et al. (2016) reported elevated systemic cytokines (IL-1β, TNF-α, IL-6) correlated with oral infection prevalence in AD and MCI patients relative to controls. Golipoor et al. (2024) compared oral fungal composition directly in AD versus non-AD patients admitted to a neurology clinic and reported 1.6-fold higher oral fungal prevalence in AD, with *C. albicans* dominant in both groups (80 percent of AD samples versus 40 percent of non-AD samples) and reduced fungal diversity in the AD samples. The reduced-diversity-with-*C. albicans*-dominance pattern in oral samples mirrors the framework's prediction for tissue-transitioning *Candida* dysregulation: as the symbiont moves toward a tissue-invasive configuration, the broader fungal community thins and the central organism becomes proportionally more dominant in the niches it has not yet vacated. The integration of oral *Candida* as one of multiple cumulative reservoirs feeding lifetime systemic exposure (gut, oral, vaginal in women, with documented translocation to brain in §III and §IV) has not been performed at the level of the integrated framework, but the oral findings considered alone already corroborate the framework's prediction that *Candida albicans* burden is differentially elevated in AD.

The gut origin section establishes the reservoir from which translocation proceeds. The framework's claim is not that any one of these inputs (diet, antibiotic exposure, sex-specific reservoir dynamics, oral burden) is sufficient on its own. The claim is that they operate continuously across a lifetime as cumulative pressure on the host-symbiont relationship,

producing the chronic age-dependent presentation of AD as the organism transitions from gut commensal to tissue-invasive form. The next section traces the translocation itself.

§III. Translocation: From Gut to System

The transition from luminal commensal to systemic dissemination is mechanistically tractable, and the published record describes the molecular machinery in detail. The framework's claim in this section is that translocation is not a rare event in compromised hosts but a continuous low-grade process in chronically dysregulated hosts, with the rate determined by gut barrier integrity, host immune competence, and the organism's morphological state.

C. albicans exists in a yeast form for commensal colonization and a hyphal form for tissue invasion. The transition between these states is governed by transcription factors including Efg1 (positive regulator of hyphal formation) and Nrg1 (negative regulator of hyphal-specific genes), and by environmental signals including pH, temperature, serum exposure, and quorum-sensing molecules. The hyphal form is not merely morphologically distinct; it expresses a transcriptional program that includes the cytolytic peptide candidalysin, the secreted aspartyl proteinases (Sap family), and adhesion factors that enable tissue invasion. The candidalysin gene *ECE1* and its peptide product have been characterized as the primary tissue-damaging factor responsible for the host barrier disruption that permits dissemination (Moyes et al. 2016).

Cornitius (2025) demonstrated the morphological and toxin requirements directly in human intestinal epithelium. Caco-2 colonic epithelial monolayers exposed to wild-type *C. albicans* showed approximately 20-fold increased permeability relative to uninfected controls. The effect required both hyphal formation and candidalysin secretion. Yeast-locked strains (*efg1*Δ/Δ, doxycycline-suppressed *tet-NRG1*) failed to disrupt the barrier. Hyphal strains lacking candidalysin (*ece1*Δ/Δ) also failed to disrupt the barrier despite forming hyphae. Complementation of the *ece1*Δ/Δ mutant with wild-type *ECE1* restored the disruption phenotype. The conclusion is that hyphal morphology alone is insufficient and toxin secretion alone is insufficient; the two are jointly required for epithelial barrier breakdown.

> [*The two-factor requirement is mechanistically informative. The organism cannot disrupt host barriers from yeast form even with candidalysin available, and cannot disrupt barriers in hyphal form without the toxin. Translocation is gated by simultaneous achievement of both states, which means the host's environment must support both the hyphal transition and the toxin expression program for translocation to occur. Chronic dysregulated states that maintain both conditions across decades produce continuous low-grade translocation rather than acute dissemination.*]

The mechanism extends to the blood-brain barrier through the same secreted aspartyl proteinases. Wu and colleagues at Baylor College of Medicine (Wu et al. 2023) demonstrated that *C. albicans* circulating in the bloodstream disrupts blood-brain barrier tight junction proteins through Sap-mediated proteolysis, and that the same Saps cleave amyloid precursor protein into

amyloid β-like peptides directly. The cleaved Aβ peptides bind Toll-like receptor 4 on microglia and activate antifungal immunity; candidalysin separately engages the integrin CD11b on microglia for fungal clearance. The mechanism is doubly significant. First, the same enzymatic apparatus that breaches the gut barrier also breaches the blood-brain barrier. Second, the molecular species that the conventional AD framework identifies as the cause of the disease (cleaved Aβ peptides) is being produced directly by the organism's own enzymes acting on host APP, with the resulting peptides serving as the host's antifungal recognition signal.

[*The Wu/Corry mechanism collapses the conventional framework's central distinction between organism-derived and host-derived pathological species. The Aβ peptides accumulating around fungal granulomas in AD brain are not host-derived molecules whose origin is unclear. They are host-derived molecules whose proximate cleavage agent is identified, characterized, and demonstrated to be a fungal enzyme. The framework's prediction is that the Saps-on-APP cleavage event in human AD brain tissue will show the same products as in the Wu/Corry mouse model, and that ratio of fungal-Sap-cleaved to host-secretase-cleaved Aβ in autopsy tissue is testable.*]

The CARD9-deficient mouse model establishes the candidalysin requirement for gut-to-brain translocation in vivo. Cornitius (2025) inoculated CARD9-knockout mice (which lack the Dectin-1 downstream signaling required for fungal clearance and are therefore permissive to colonization) with either wild-type *C. albicans* or *ece1*Δ/Δ candidalysin-deficient strain. After four days, brain CFU assays detected wild-type fungus in brain homogenate; the candidalysin mutant did not establish brain colonization. The mechanism of translocation is therefore identified at the level of the toxin: candidalysin secretion enables the fungus to traverse from gastrointestinal lumen to systemic circulation to brain parenchyma. In the immunocompromised host, this is the operative mechanism.

The complication, which the framework reads as confirming rather than weakening the model, emerges in the genetically AD-susceptible host. APP-NLGF transgenic mice carry humanized APP with Swedish, Iberian, and Arctic mutations producing chronic Aβ overproduction and the amyloid pathology characteristic of familial AD. Cornitius found that these mice have constitutively elevated gut permeability and dysregulated cytokine expression at baseline relative to wild-type littermates. Inoculated with *C. albicans*, the APP-NLGF mice supported gut colonization independent of candidalysin: both wild-type and *ece1*Δ/Δ strains established stable colonization following antibiotic-induced dysbiosis, with the wild-type achieving roughly 2-log higher density. The interpretation within the framework is that candidalysin is the disruption tool when the host barrier is intact. When the host has constitutive barrier dysfunction (as in the APP-NLGF model and, the framework predicts, in chronically dysregulated human hosts approaching AD onset), the toxin requirement is relaxed because the disruption is already present.

[*The shift from candidalysin-required to candidalysin-independent colonization across host genetic backgrounds is the framework's prediction operationalized. The AD-genetic-background host presents a pre-disrupted gut barrier that any Candida can colonize. The toxin is the tool that creates the disruption in healthy hosts. In hosts approaching AD onset, the disruption is already present from chronic accumulated dysregulation, and the organism's translocation no longer depends on the same toxin profile. This explains why epidemiological associations between Candida exposure and AD are not gated by candidalysin-positive strain identification, and why the candidalysin-independence in advanced disease is not evidence against fungal involvement.*]

Translocation is detectable systemically. Alonso, Pisa, and colleagues (Alonso et al. 2014) tested 29 AD patients and matched controls for systemic disseminated fungal markers. Twenty-eight of 29 AD patients showed Fungitell-positive serum, indicating detectable circulating fungal (1,3)-β-glucan. Eleven of 29 showed high immunoreactivity against multiple *Candida* species; an additional two showed high reactivity against a single *Candida* species. The serum signal is a peripheral marker of the dissemination state. AD patients are not in localized brain infection; they are in systemic disseminated mycosis with the brain as one of several affected compartments.

The cerebrospinal fluid signal corroborates and extends this finding. Alonso et al. (2015) demonstrated fungal antigens in CSF samples from 10 of 10 AD patients and 0 of 3 controls ($p=0.0016$, OR=8). Six of these samples were sequenced for fungal DNA via internal transcribed spacer (ITS) regions, and four contained multiple fungal species. The multi-species CSF finding has two implications. First, it corroborates the framework's prediction (Prediction D, queued as a separate Architect Report) that multi-genus fungal presence is a structured rather than random feature of chronic dysregulation. Second, it identifies a diagnostic pathway available in living patients. Lumbar puncture is a well-developed clinical procedure with known risk profile, deployed in neurology and infectious disease practice when the diagnostic question justifies the procedural burden; slot-blot fungal antigen detection is established mycology laboratory technique; ITS sequencing is widely available. The methods for in vivo fungal-AD characterization in appropriately selected patients therefore exist. The framework's reading of why this characterization has not entered clinical use, even selectively, is treated in §X.

The vasculature is itself a translocation compartment. Pisa et al. (2015) documented fungal cells of varying sizes and hyphae inside cerebral capillaries and other CNS blood vessels, with additional staining in vessel walls, across multiple AD patients. Approximately 90 percent of AD patients exhibit cerebrovascular pathology including cerebral amyloid angiopathy, microinfarcts, microhemorrhages, and microvascular degeneration. The conventional framework treats these as independent vascular pathology, with amyloid β deposits in capillary walls forming cerebral amyloid angiopathy through mechanisms parallel to the parenchymal plaque

process. The framework's reading is that vessel-wall amyloid co-localizes with what it is encapsulating: the fungal cells and hyphae documented in those same vessels by Pisa.

> [*Cerebral amyloid angiopathy is reframed within the framework as encapsulation of vascular fungal infection rather than independent vascular pathology. The 90 percent prevalence of vascular involvement in AD is consistent with the dissemination architecture: the organism arrives via the circulation, deposits preferentially in vessel walls and capillary beds, and the host encapsulates it where it lodges. The amyloid signal in the vasculature is the same antimicrobial encapsulation signal as the parenchymal plaque, deployed against the same target in a different compartment. This reading has direct therapeutic implications, treated in §V regarding the amyloid-related imaging abnormalities profile of current anti-amyloid antibody therapy.*]

The vasculature, the parenchyma, and the cerebrospinal fluid are not the deepest compartments the organism reaches. Pisa and colleagues documented fungal bodies inside neurons and within neuronal nuclei across multiple brain regions, a finding with mechanistic implications that §IV develops in full. [*Raise your hand if you thought C. albicans could invade a cell and takeover – Me…hand raised since 1995*]

The translocation chapter establishes that the published mechanism is sufficient to account for the documented presence of *C. albicans* in AD brain tissue, in CSF, in serum, and in vasculature simultaneously. The organism's molecular machinery for traversing host barriers is identified. The host's permissive states (immunocompromise via CARD9-pathway disruption, constitutive barrier dysfunction in AD-genetic backgrounds, chronic accumulated dysregulation in older adults) are characterized. The systemic signal is detectable in living patients through existing clinical assays. The next section documents what arrives at the destination.

§IV. Brain Colonization: The Documented Reality

The brain colonization data has accumulated across more than a decade in major peer-reviewed venues. The conventional AD framework treats this body of evidence as parallel to the field rather than central to it, with the result that few practitioners and few clinical investigators are aware of the specific findings. This section assembles the documented colonization architecture as an integrated record.

IV.1 Human Postmortem Evidence

The foundational human evidence rests on the Carrasco group at Centro de Biología Molecular Severo Ochoa (Madrid). Across a series of papers from 2014 onward, this group established that *C. albicans* and several other fungal genera are detectable in postmortem brain tissue from patients diagnosed with Alzheimer's disease, with absent or minimal signal in age-matched controls. Alonso et al. (2014) demonstrated fungal proteins in AD brain through proteomic analysis, fungal DNA through PCR amplification with subsequent sequencing

identifying multiple species, and the foundational claim that "to our knowledge these findings represent the first evidence that fungal infection is detectable in blood and brain samples from AD patients." Pisa et al. (2015) extended this to multi-region characterization across external frontal cortex, cerebellar hemisphere, entorhinal cortex/hippocampus, and choroid plexus, with fungal cells and hyphae visualized using antibodies against five distinct fungal species. Eleven AD patients plus three additional choroid plexus samples were positive in 100 percent of cases; ten matched controls were negative in 100 percent of cases. [*Math made easy..right?*]

The architecture of brain colonization is therefore not a probabilistic risk factor in AD; in the patients sampled by Pisa's group, it is a categorical finding. Every AD brain examined showed fungal infection. No control brain examined did. Subsequent work from the same group (Alonso et al. 2018) extended the finding through next-generation sequencing across larger cohorts, identifying *Alternaria*, *Botrytis*, *Candida*, and *Malassezia* as the most prominent genera in AD samples, with distinct compositional patterns relative to elderly controls and to younger subjects.

> [*The 100 percent versus 0 percent observation in the Pisa cohort is what a categorical disease etiology looks like before it has been recognized as such. Cross-sectional case-control studies of established etiological agents (Helicobacter pylori in ulcers, HPV in cervical cancer) showed similar patterns at the moment the etiology was being established. The conventional AD framework absorbs the 100/0 finding as "fungi in AD brain may be a consequence of disease-related immune compromise," which is the standard secondary-pathogen reading. The framework reads it as foundational.*]

IV.2 Animal Model Causation

Wu, Corry, and colleagues at Baylor College of Medicine established the causal direction in mouse models. Wu et al. (2019) injected wild-type mice with 25,000 *C. albicans* yeast cells via tail vein and demonstrated that the organism crossed the blood-brain barrier without exogenous facilitation, established what the authors named "fungus-induced glial granulomas" (FIGGs) characterized by hypertrophic activated microglia surrounding yeast aggregates, and induced accumulation of amyloid precursor protein at the periphery of these granulomas with cleaved Aβ peptides accumulating around the central yeast cells. The infected mice exhibited measurable spatial memory impairment that correlated with FIGG presence and resolved with fungal clearance. The architecture of the FIGG, with concentric microglial activation, peripheral APP, and central Aβ deposition around fungal cores, is morphologically indistinguishable from the cored amyloid plaques of human AD brain, with the difference that the fungal core is visible because the experimental design preserved it for visualization.

The follow-up work (Wu et al. 2023) characterized the mechanism in molecular detail. *C. albicans* secreted aspartyl proteinases hydrolyze tight-junction proteins of the blood-brain barrier to permit entry. The same Saps cleave host APP into Aβ-like peptides that bind microglial Toll-like receptor 4 and activate antifungal immunity. Candidalysin separately engages microglial

CD11b to drive fungal clearance. In healthy mice, the infection resolves within approximately 10 days. The FIGGs and associated Aβ deposition persist for at least 21 days post-clearance. The cellular memory of the infection (architectural Aβ deposition) outlasts the fungal load by a substantial interval.

The Cornitius (2025) UTSA dissertation extended this work into human iPSC-derived cortical organoids with controlled glial composition. *C. albicans* infiltrated organoids at all developmental stages, with cell-type-specific responses: astrocyte-containing organoids exhibited increased IL-6 expression in response to hyphal forms (independent of candidalysin), while microglia-containing organoids showed minimal inflammatory cytokine response, suggesting that microglia mediate fungal clearance through the candidalysin-CD11b pathway documented in mice. PSEN1 L435F familial AD organoids without glia showed elevated baseline Thioflavin S signal (amyloid β β-pleated sheet structure) and increased ThioS deposition when challenged with candidalysin-deficient strains. The organoid system therefore reproduces in human neural tissue the architectural elements of the mouse model: the cell-type-specific division of labor between microglial clearance and astrocytic inflammation, the connection between fungal challenge and amyloid signal, and the modulation of these effects by host genetic background.

[*The FIGG architecture in Wu/Corry's mouse model is the same morphological structure conventionally identified as a senile plaque in AD brain. The conventional framework treats senile plaques as protein aggregates of host origin; the Wu/Corry mechanism demonstrates that the same architecture forms around live fungal cores when fungi are present. The framework's prediction is that human cored plaques, examined with adequate fungal staining, will show fungal material at their centers in a substantial fraction of cases. Pisa's intranuclear and intracellular findings (treated below) and the broader brain colonization evidence support this prediction; targeted reanalysis of plaque architecture in AD autopsy tissue with fungal-specific staining is one of the simpler experimental tests the field could perform.*]

IV.3 Cerebrospinal Fluid in Living Patients

Brain colonization evidence is not limited to postmortem analysis. Alonso et al. (2015) demonstrated fungal proteins and DNA in CSF from living AD patients. Slot-blot analysis with multiple anti-fungal antibodies was positive in 10 of 10 AD patients and 0 of 3 controls ($p=0.0016$, OR=8). DNA sequencing of fungal ITS regions identified six fungal genera, with four of six AD samples showing multi-species composition. The diagnostic architecture is established. Lumbar puncture is a well-developed clinical procedure with a known risk profile, performed across neurology and infectious disease practice when the diagnostic question justifies the procedural burden. Slot-blot fungal antigen detection is standard mycology laboratory technique, and ITS sequencing is widely available. In vivo fungal-AD characterization is therefore technically tractable in living patients today, though the procedural cost of CSF

acquisition means the test would be appropriately deployed in selected cases rather than universally. It is not currently part of standard AD workup.

IV.4 The Intracellular and Intranuclear Position

The most architecturally significant finding in the Pisa series, and the finding most resistant to absorption by the conventional AD framework, is the demonstration of fungal bodies inside host neurons and inside neuronal nuclei. Pisa et al. (2015) reported: "In some instances, fungal cells were clearly visible inside neurons and exhibited an intranuclear location as indicated by counterstaining with the DNA stain, 4',6-diamidino-2-phenylindole (DAPI)." The intranuclear localization was documented across multiple brain regions (external frontal cortex, cerebellar hemisphere, entorhinal cortex/hippocampus) and across multiple antibody panels (anti-*C. glabrata*, anti-*C. famata*, anti-*C. albicans*, anti-*P. betae*, anti-*S. racemosum*). The fungal cells co-stained with DAPI, indicating that the structures observed in neuronal nuclei contained fungal nucleic acid. [*Hand still raised*]

The conventional categories of mycology and neuropathology have no clean place for this finding. Most fungal infections of the central nervous system are extracellular (cryptococcal meningitis, aspergillosis), with phagocytic uptake by macrophages constituting the principal intracellular residence. Intracellular *Candida* in macrophages and dendritic cells is documented in mucosal infection biology. Intracellular *Candida* in non-immune host cells is less commonly described, and intranuclear localization in postmitotic neurons is, to our knowledge, not described elsewhere in the literature. The Pisa finding has not been systematically replicated by independent groups, but it has not been refuted either; it has been ignored.

> [*The intranuclear position is the framework's strongest single anatomical claim about the host-symbiont relationship in chronic disease. From inside the host cell nucleus, the organism is no longer subject to the host's compartmental defenses. It has access to the host's transcriptional machinery, can release nucleic acids and effector proteins into the genomic compartment, can interact with chromatin directly, and can drive host cellular fate decisions including apoptosis. The architectural inference is that chronic AD is not the host failing to clear an extracellular pathogen but the host living with an organism that has reached the deepest functional position available in its cellular architecture. From this position, the organism is in a category beyond infection in the conventional sense: it is operating inside the regulatory compartment of the cells whose function defines the disease. It is driving the car.*]

The mechanistic implications are not speculative. *C. albicans* is documented to release extracellular vesicles containing RNA species, proteins, and metabolites that modulate host cell function (Vargas et al. 2015; Peres da Silva et al. 2019). The organism's secreted aspartyl proteinases process host proteins including APP. The organism's chromatin state machinery, characterized in Paper A (Craddock, Biochemical Computer) as multi-acyl-CoA-responsive transcriptional architecture, is the same architectural class as the H3K9 lactylation machinery

treated in §VI for host astrocytic dysfunction, with the difference that the organism's machinery is operating from inside host nuclei when the intranuclear configuration is established. The combination of physical access to the host genome, enzymatic apparatus for processing host proteins, and metabolic-epigenetic signaling architecture provides the operational basis for the framework's claim that chronic dysregulation in this configuration produces stuck-state disease through manipulation of host cellular state from the most privileged position in the cell.

The clinical implications follow. From the intranuclear position, induction of host cell apoptosis is mechanistically straightforward: the organism has direct access to the regulatory compartment that controls cell death programs. The chronic neuronal loss characteristic of AD progression is, in the framework's reading, partly produced by organism-mediated apoptotic induction in the host neurons it has colonized. The component pieces of this claim are present in the published literature. Apoptotic signatures in AD-affected brain regions are well-characterized, with documented mitochondrial pathway activation, caspase cascade involvement, and additional regulated cell death modalities including necroptosis, pyroptosis, and ferroptosis (Goel et al. 2022). Intraneuronal and intranuclear fungal localization in those same regions is documented by Pisa et al. (2015). The specific dual-staining analysis combining fungal staining with TUNEL or comparable apoptotic markers on the same sections in an adequately powered AD cohort has not been performed to the framework's knowledge. The framework's prediction is that such an analysis would show co-localization between intranuclear fungal presence and apoptotic signature in residual neurons, with the magnitude of co-localization tracking regional neuronal loss. The prediction is testable in autopsy tissue using existing fungal staining methodology and standard apoptotic markers.

> [*The framework's claim that intranuclear C. albicans can drive host neuronal apoptosis is a strong claim that is not yet directly demonstrated in autopsy tissue. It is consistent with the mechanistic capabilities documented for the organism in vitro and with the architectural finding documented by Pisa. The empirical question of whether this mechanism operates in human AD brain is open. The framework treats it as the natural extension of the documented findings; the dual-staining test that would address it has not been performed.*]

IV.5 Co-Infection Architecture and the Polymicrobial Reading

A separate body of literature has independently arrived at a "polymicrobial" or "multi-pathogen" hypothesis of AD, with fungi, bacteria (especially periodontal pathogens including *Porphyromonas gingivalis* and various spirochetes), and viruses (especially herpetic viruses HSV-1, HHV-6, HHV-7) all proposed as contributors. Vigasova et al. (2021) consolidated this literature with extensive citation.

The framework's reading subsumes the polymicrobial picture rather than competing with it. *C. albicans* biofilms are documented to shelter other pathogens including HSV-1, with the viruses remaining infective and releasable from within the biofilm matrix (Mazaheritehrani et al.

2014). The biofilm architecture is polymicrobial by construction; bacterial species and fungal species co-occupy and co-stabilize biofilm communities (Tsui et al. 2016). The "polymicrobial AD" researchers are detecting real signal: multiple pathogens are present in AD brain. The framework's claim is that the multiple pathogens are not independent etiological agents but passengers in *Candida*-architected biofilms, with the fungus as the structural organism and the bacterial and viral species protected within. Itzhaki's HSV-1 work (Itzhaki et al. 1997)10149-5; Itzhaki 2021) and Dominy's *P. gingivalis* work (Dominy et al. 2019) and Pisa's fungal work each describe genuine components of the same architecture; the integration the field has not made is that the components co-exist within a single fungal-architected structure rather than competing as separate hypotheses.

The clinical implication is that polymicrobial AD therapy, which the field has occasionally proposed, would need to begin with antifungal coverage to address the architect organism rather than the passengers. The Loeb 2004 trial (rifampin + doxycycline) and the Tzeng 2018 antiviral data (treated in §VII) likely produce their observed cognitive effects through partial coverage of biofilm passengers without disrupting the fungal architecture, which would predict modest benefit followed by recurrence. Antifungal therapy would predict more durable response if the framework's reading is correct.

> [*The polymicrobial reading has been treated by some commentators as competing with the fungal hypothesis. The framework's claim is that the polymicrobial reading is correct in its empirical observations and incomplete in its architectural inference. Multiple pathogens are present; one of them is structurally central. This integrates rather than displaces the existing polymicrobial literature.*]

IV.6 Summary

The brain colonization architecture, as documented in the published record, includes the following established and probable elements: presence of fungal cells and hyphae across multiple brain regions in 100 percent of AD patients sampled (Pisa et al. 2015); systemic disseminated fungal antigen in serum of 28 of 29 AD patients (Alonso et al. 2014); fungal antigens in CSF of 10 of 10 living AD patients (Alonso et al. 2015); causal demonstration in mouse models with characteristic glial granuloma architecture and amyloid β deposition (Wu et al. 2019, 2023); intracellular and intranuclear residence in human host neurons (Pisa et al. 2015); cell-type-specific responses in human iPSC-derived cortical organoids (Cornitius 2025); polymicrobial co-occupation of fungal-architected biofilms (Mazaheritehrani et al. 2014); and translocation mechanism through fungal Saps and candidalysin from gut and from circulation (Wu et al. 2023; Cornitius 2025). The architecture is not partial, not speculative, and not localized to one research group. It is documented, multi-source, and accumulated over more than a decade. [*Tell me who is driving?*] The next section addresses what the host does in response, and why the response has been misread.

§V. Aβ as Defensive Encapsulation: Reframing the Plaque

The reframe in this section is the architectural inversion that makes the rest of the framework's reading of AD coherent. The conventional hypothesis treats amyloid β plaques as misfolded protein aggregates whose accumulation drives neurodegeneration, with their removal expected to halt or reverse the disease. The framework reads amyloid β plaques as antimicrobial defensive encapsulation around live brain pathogens, with their removal predicted to compromise host defense without addressing the underlying organism. The two readings predict opposite outcomes from the same therapeutic intervention. The clinical record decides between them.

V.1 Aβ as Antimicrobial Peptide

The framework's reading is not based on a novel claim about amyloid β biochemistry. The antimicrobial peptide function of Aβ is established in the published literature, by investigators working within the conventional AD framework, with results that the conventional framework has not integrated.

Soscia, Tanzi, and colleagues at Massachusetts General Hospital (Soscia et al. 2010) demonstrated that Aβ has direct antimicrobial activity against multiple pathogens including *Candida albicans*, *Streptococcus pneumoniae*, *Listeria monocytogenes*, *Staphylococcus epidermidis*, *Escherichia coli*, and others, with antimicrobial potency comparable to LL-37, the canonical human cathelicidin antimicrobial peptide. The activity against *C. albicans* was particularly strong; Aβ is among the more potent endogenous antifungal peptides characterized in human biology. The mechanism involves Aβ oligomerization in the presence of microbial surfaces, with the oligomeric forms (the species conventionally identified as the most pathogenic in AD) constituting the most active antimicrobial conformations.

Kumar and colleagues (Kumar et al. 2016) extended this finding to live infection. In transgenic mouse and *Caenorhabditis elegans* models of AD, Aβ expression protected against *Salmonella typhimurium* and *C. albicans* infection respectively. APP/PS1 mice expressing humanized Aβ survived intracerebral *S. typhimurium* challenge significantly better than wild-type controls. The protective Aβ formed antimicrobial fibrils that physically entrapped pathogens. The same fibril architecture that the conventional framework identifies as pathogenic plaque material was, in this experimental context, demonstrated to be protective antimicrobial encapsulation.

Eimer, Tanzi, and colleagues (Eimer et al. 2018) extended this further to viral infection. HSV-1 infection of the mouse brain seeded Aβ deposition rapidly, with the seeded Aβ binding to and entrapping HSV-1 virions. The deposition was protective: 5xFAD mice expressing humanized Aβ survived HSV-1 infection significantly better than non-transgenic controls. The conclusion drawn by the authors, framed within the conventional AD literature, was that "Aβ may be one component of an innate immune response to brain infection." The framework reads

this as the same finding stated more weakly: Aβ is the deployed antimicrobial defense, and amyloid plaque architecture is what the host produces when the defense is deployed.

[*Three independent demonstrations across more than a decade establish Aβ as a functional antimicrobial peptide whose deployment produces architectural structures morphologically identical to the senile plaques of AD. The conventional framework treats these findings as adjacent to the disease question rather than central to it. The framework treats them as the disease question, with the reframe consisting of taking the antimicrobial finding seriously: the plaques are doing their job, and the disease is what happens when the host is in chronic deployment of antimicrobial defense against an organism the host cannot clear. Pretty Cool, huh?*]

V.2 The Wu/Corry Mechanism: Aβ as Deployed Defense

The Wu/Corry work treated in §III and §IV provides the mechanism by which Aβ encapsulation forms around fungal targets in vivo. The relevant findings are summarized here for the encapsulation argument: *C. albicans* injected into mouse circulation crosses the blood-brain barrier through Sap-mediated proteolysis of tight junction proteins; the same Saps cleave host APP into Aβ-like peptides directly; the cleaved Aβ deposits around yeast cells at the centers of forming granulomas; the resulting fungal-induced glial granulomas (FIGGs) are morphologically indistinguishable from cored amyloid plaques of human AD brain, with the fungal core preserved for visualization in the experimental design (Wu et al. 2019; Wu et al. 2023).

The architecture produced is the architecture observed in human AD postmortem tissue. The plaque is what the host produces when fungal cells lodge in brain parenchyma. The Aβ surrounding the fungal core is the host's antimicrobial defense deployed against the live pathogen at the center. The microglial activation is the cellular component of the antifungal immune response. The conventional framework views this architecture and identifies the host defensive response as the disease. The framework views the same architecture and identifies the encapsulated organism as the disease, with the host response as appropriate but failed defense.

V.3 Anti-Amyloid Trial Failures

The reframe predicts a specific therapeutic outcome from anti-amyloid antibody therapy. If amyloid plaques are antimicrobial defensive encapsulation around live brain pathogens, then antibody-mediated amyloid clearance should produce visible biomarker improvement (PET-detectable amyloid reduction) without functional benefit (cognition unchanged), because the proximate cause of the cognitive decline (the encapsulated organism) is not addressed by the therapy. The therapy removes the host's defensive structure while leaving the target of that defense in place. The clinical record produced by anti-amyloid antibody therapeutics matches this prediction with unusual precision.

The DIAN-TU trial (Salloway et al. 2021) tested gantenerumab and solanezumab in patients with dominantly inherited Alzheimer's disease across asymptomatic and symptomatic

stages, with treatment durations of 4 to 7 years. Both drugs engaged their Aβ targets. Gantenerumab significantly reduced amyloid plaque burden as measured by PET. Neither drug produced cognitive benefit on the primary cognitive endpoints. The decoupling of biomarker engagement from functional outcome was complete.

The A4 secondary prevention trial (Sperling et al. 2023) tested solanezumab in 1,150 cognitively unimpaired adults aged 65 to 85 with elevated brain amyloid on PET, treated for 240 weeks. Solanezumab did not slow cognitive decline relative to placebo. The placebo group performed marginally better than the solanezumab group on the primary cognitive composite, with the difference not reaching statistical significance.

The GRADUATE 1 and 2 Phase 3 trials of gantenerumab in early symptomatic AD (Bateman et al. 2023) enrolled 985 and 980 participants respectively. Both trials failed their primary cognitive endpoints, with CDR-SB differences of -0.31 and -0.19 between treatment and placebo at 116 weeks, statistically insignificant. Gantenerumab also produced less amyloid plaque reduction than expected based on earlier studies.

The lecanemab Clarity AD trial (van Dyck et al. 2023), the basis for FDA approval, enrolled 1,795 patients with early symptomatic AD. The treatment group showed a 0.45-point CDR-SB difference relative to placebo at 18 months, on an 18-point scale. The 0.45-point difference is below the minimum observable change on the CDR-SB (0.5 points), and below most published thresholds for minimum clinically important difference. The 27 percent slowing of cognitive decline figure prominently reported represents this 0.45/1.66 ratio. Critically, the supplementary analysis (addressed by Imbimbo et al. 2024) showed that lecanemab did not produce benefit in women, who comprise approximately two-thirds of AD patients, and did not produce benefit in APOE4 carriers, who comprise 60 to 75 percent of AD patients. The treatment effect was concentrated in male non-APOE4 carriers, a small subgroup of the overall AD population.

The donanemab TRAILBLAZER-ALZ 2 trial (Sims et al. 2023) reported a 0.68-point CDR-SB difference at 76 weeks, slightly larger than lecanemab but with the same fundamental architecture: substantial amyloid clearance, modest cognitive effect, concentrated benefit in subpopulations.

A comprehensive evidence review of 17 trials encompassing more than 20,000 participants concluded that the absolute effects of anti-amyloid antibodies on cognitive decline and dementia were "absent or trivial," falling below standard thresholds for clinical effectiveness (Nonino et al. 2026). The aggregate finding across the entire program is that biomarker engagement is reliably achievable, amyloid clearance is reliably achievable, and cognitive benefit is at best marginal and at worst absent.

[*The conventional amyloid hypothesis predicts that removing the proximate cause should restore function. The clinical record demonstrates the opposite. The amyloid hypothesis has been the most extensively tested causal hypothesis in modern neurology,*

with cumulative pharmaceutical investment in the tens of billions of dollars, and the test results across multiple drug classes, multiple patient populations, and durations exceeding seven years are consistent: removing the proxy does not change the disease. The framework's prediction is exactly this outcome. The amyloid is not the cause; it is the encapsulation. Removing the encapsulation does not address the encapsulated organism, and the disease continues.]

V.4 ARIA as Encapsulation-Stripping Signature

The major adverse event class associated with anti-amyloid antibody therapy is ARIA (amyloid-related imaging abnormalities), occurring at substantially elevated rates relative to placebo. ARIA-E (edema) and ARIA-H (hemorrhage and hemosiderosis) together affect approximately 20 to 30 percent of treated patients depending on the specific antibody, dose, and APOE4 status. The risk is concentrated in APOE4 homozygotes, in whom ARIA rates can approach 40 percent. Severe ARIA cases include macrohemorrhages, some fatal. Lecanemab-associated and donanemab-associated patient deaths from ARIA-related complications are documented in the post-approval clinical record.

The conventional framework treats ARIA as an adverse pharmacological consequence of vascular amyloid mobilization, with the antibody dissolving cerebral amyloid angiopathy deposits and producing local inflammation and microvascular fragility. This interpretation is mechanistically correct as far as it goes. The framework extends it. The cerebral amyloid angiopathy (vascular amyloid deposition) co-localizes with the fungal cells and hyphae documented by Pisa et al. (2015) in CNS blood vessels and vessel walls. If vascular amyloid is encapsulation around vascular fungal infection, then antibody-mediated dissolution of vascular amyloid produces exposure of live fungal material in the cerebral vasculature, with subsequent local inflammation, vessel wall fragility, microhemorrhage, and edema as the predicted sequelae. The ARIA pattern is the encapsulation-stripping signature.

The prediction is testable. Autopsy tissue from patients who died from severe ARIA on anti-amyloid antibody therapy should show, on adequate fungal staining, increased detection of fungal material in cerebral vasculature relative to comparable AD patients not on antibody therapy. The hemorrhagic foci should localize with vessel wall fungal deposits. The framework's prediction is positive correlation between ARIA severity and vascular fungal burden. The conventional framework predicts no such correlation, since fungi are not part of its model. The autopsy infrastructure exists; the antibodies necessary for fungal staining are commercially available; the question has not been asked.

[*ARIA is the pattern that distinguishes the framework's reading from the conventional reading most cleanly. Both readings predict adverse vascular events from antibody-mediated amyloid mobilization. The framework predicts that the events will correlate with fungal burden in the affected vasculature; the conventional reading predicts that the events will correlate with cerebral amyloid angiopathy severity but not*

with fungal presence. The autopsy correlation is testable and would discriminate between the two frameworks directly.]

V.5 The Asymptomatic Amyloid Carriage Finding

Approximately 30 percent of cognitively normal adults over age 70 have detectable brain amyloid by PET scanning, with the proportion rising to 50 percent or more in cognitively normal adults over 85 (Jansen et al. 2015). The conventional framework identifies these individuals as being in "preclinical AD," a presymptomatic stage of the disease. The framework reads them differently. If amyloid is encapsulation, then asymptomatic amyloid carriage indicates effective ongoing antimicrobial defense: the host is encapsulating fungal material successfully, the encapsulation is producing the PET signal, and the system is functioning as defense rather than as disease. The transition to symptomatic AD, in the framework's reading, is not the accumulation of amyloid passing a threshold; it is the failure of the host's clearance and inflammatory regulation systems, treated in §VI, that converts effective encapsulation into chronic dysfunctional inflammation.

This reading explains a finding the conventional framework treats as paradoxical: the population-level dissociation between amyloid burden and cognitive status. Many high-amyloid individuals are cognitively intact; many cognitively impaired individuals have modest amyloid; the correlation at the individual level is weaker than the conventional framework predicts. Within the framework, amyloid is a marker of host defensive activity, not a marker of disease severity. Symptomatic AD requires both substantial encapsulated organism load and failure of the host compensation systems that maintain the encapsulation in functional rather than dysfunctional state. The two variables are partially independent, which is why amyloid burden alone does not predict cognitive status. [*Are you following me? Working as intended.*]

V.6 Bridge to the Astrocytic Compartment

The encapsulation reframe explains why anti-amyloid therapeutics produce biomarker improvement without functional benefit. It does not yet explain why some hosts maintain effective encapsulation across decades while others progress to symptomatic disease. Two carriers can have similar fungal burden and divergent outcomes; APOE4 status, sex, and age account for some of the variance, but the cellular architecture of the host's encapsulation and clearance machinery has not been examined directly. The framework predicts that a specific transcription factor program governs astrocytic phagocytic clearance of fungal material, and that program's failure mode produces the chronic-progressive trajectory characteristic of late AD. Three independent lines of evidence published since 2022 converge on a single transcription factor architecture in astrocytes. Read together, they supply the cellular mechanism for the encapsulation-clearance failure the framework predicts. [*This science stuff is pretty cool.*]

§VI. The Astrocytic Compartment: SOX9-MEGF10-Hk1

VI.1 The Convergence

Three independent research programs published between 2022 and 2025 converge on a single transcription factor architecture in astrocytes. None of the three was framed as a contribution to fungal-AD theory. None of the three integrates with the others in their original publications. Read together, they supply the cellular mechanism for the encapsulation-clearance failure that distinguishes asymptomatic amyloid carriage from symptomatic AD.

The convergence point is SOX9, a transcription factor expressed in adult brain almost exclusively by astrocytes (Sun et al. 2017). SOX9 is not a novel target; its astrocyte specificity has been established for nearly a decade and its developmental and homeostatic roles have been characterized across neuroscience and developmental biology. What is novel, and what the conventional AD framework has not integrated, is that SOX9 in adult astrocytes runs at least two parallel transcriptional programs with opposing consequences for AD pathology, and that the host's chronic *Candida* exposure produces a documented mechanism for selectively disabling one program while leaving the other intact. The asymmetric disabling converts SOX9 from a maintenance transcription factor into a driver of the chronic inflammatory state that characterizes symptomatic AD.

> [*The SOX9-MEGF10-Hk1 architecture is the framework's most specific cellular mechanism claim about AD progression. It predicts a specific decoupling between SOX9 transcript and SOX9 protein function in chronic-Candida hosts, with the decoupling producing the failure mode that converts encapsulation into disease. The prediction is testable through the biomarker triad treated in §IX. The framework's claim is that this mechanism, integrated from three independent labs, supplies the missing piece that conventional AD pharmacology has been unable to specify.*]

VI.2 SOX9 to MEGF10: The Phagocytic Clearance Arm

Choi, Deneen, and colleagues at Baylor College of Medicine (Choi et al. 2025) demonstrated that astrocytic SOX9 transcriptionally activates MEGF10, a phagocytic receptor responsible for engulfment of debris and protein aggregates. In AD mouse models with established amyloid pathology and cognitive impairment, astrocyte-specific overexpression of SOX9 produced clearance of existing amyloid plaques through MEGF10-mediated phagocytosis and preserved cognitive function. SOX9 deletion produced the opposite effect: reduced phagocytic capacity, faster plaque accumulation, faster cognitive decline. The therapeutic intervention worked when applied to mice already exhibiting symptoms, indicating that the phagocytic clearance arm is operationally available even in late-stage disease in this clean experimental system.

The mechanism is direct. SOX9 binds the MEGF10 promoter and drives transcription. MEGF10 protein on astrocyte surfaces engages amyloid β through its phagocytic recognition domains. The amyloid is engulfed and processed. Plaques shrink. Cognition holds.

Within the framework, this is the architecture of the host's amyloid clearance system functioning correctly. The astrocytic compartment is not merely a structural support tissue; it is the host's ongoing maintenance system for the antimicrobial encapsulation deployed in §V. When fungal cells lodge in brain parenchyma and the host deploys Aβ as defensive encapsulation, the astrocytic SOX9-MEGF10 axis is the system that subsequently processes the encapsulation: it phagocytoses the encapsulated material, removes it from the parenchyma, and presumably enables clearance of both the amyloid and the encapsulated organism. In a clean mouse system without chronic systemic *Candida* dysregulation, this axis works efficiently. The Choi/Deneen finding is what the system looks like operating as designed.

VI.3 SOX9 to Hk1 to Lactate to H3K9 Lactylation: The Inflammatory Arm

Chen and colleagues (Chen et al. 2025) characterized a parallel SOX9 transcriptional program in astrocytes operating through hexokinase-1 (Hk1), the rate-limiting enzyme of glycolysis. The work was performed in a rat model of neuropathic pain rather than AD, but the mechanism is generalizable across reactive astrocyte states. SOX9 transcriptionally activates Hk1; elevated Hk1 drives high-rate astrocytic glycolysis; the resulting lactate output drives histone H3K9 lactylation; H3K9 lactylation activates transcription of pro-inflammatory and neurotoxic gene programs; the activated transcription drives a pathogenic astrocyte state with sustained inflammatory output.

The loop is metabolic-epigenetic. Lactate produced by glycolytic astrocytes is converted to lactyl-CoA, which is incorporated into histone modifications by acetyltransferase machinery, which alters chromatin accessibility at inflammatory gene promoters, which produces the transcriptional output that defines the pathogenic astrocyte state. The mechanism is a self-amplifying feedback loop: inflammatory state drives SOX9 elevation, SOX9 drives Hk1 elevation, Hk1 drives lactate, lactate drives chromatin modification, chromatin modification drives inflammatory transcription, and the cycle continues until something interrupts it.

The Chen work identified the loop in neuropathic pain, where reactive astrocytes drive chronic spinal dorsal horn inflammation. The framework's claim is that the same loop operates in AD-affected hippocampal and cortical astrocytes, where chronic *Candida* dysregulation produces the upstream stress that initiates and sustains the cycle. The Alamoudi computational analysis of human AD brain transcriptomic data (Alamoudi 2023) supports this extrapolation: SOX9 is elevated in human AD brains, the elevation correlates with Braak stage progression, and SOX9 expression in AD brains negatively correlates with oxidative phosphorylation gene expression. The negative OXPHOS correlation is the metabolic shift the Chen loop predicts: astrocytes shifting away from oxidative phosphorylation toward glycolysis, producing lactate, driving H3K9 lactylation, locking in the pathogenic transcriptional state.

A complementary observation in human AD comes from Bell et al. (2025). iPSC-derived astrocytes from sporadic AD patients show HK1 expression deficits, impaired glycolysis, mitochondrial dysfunction, and reduced lactate shuttling support for neurons; HK1

overexpression rescues the metabolic phenotype in sporadic AD astrocytes (though not in familial AD). The Bell finding initially reads as in tension with the Chen mechanism: Chen documents pathological HK1 elevation driving inflammation in reactive astrocyte subsets, while Bell documents HK1 deficit in bulk sporadic AD astrocytes. The framework reads these findings as complementary rather than contradictory. AD astrocyte populations are heterogeneous. Bulk-tissue iPSC-derived sporadic AD astrocyte measurements capture the dominant homeostatic/support-failure phenotype, in which chronic governance stress drives astrocytes toward an exhausted state with reduced HK1 expression and impaired neuronal support. Single-cell and injury-context measurements (Chen's reactive astrocyte subsets) capture the minority inflammatory subpopulation, in which SOX9 phosphorylation drives HK1 hyper-activation and H3K9-lactylation-mediated inflammatory locking. SOX9 functions as a master rheostat that, under chronic *Candida* governance stress, bifurcates astrocyte responses: some cells with insufficient activation develop HK1 deficits (Bell phenotype), others with aberrant SOX9 phosphorylation lock into the SOX9-Hk1-H3K9la inflammatory loop (Chen phenotype). Both populations coexist in the same diseased brain, describing a bifurcated, non-resolving astrocyte response: support failure plus pathological hyper-reactivity, both driven by the same upstream SOX9 dysregulation. The framework's specific architectural prediction beyond either paper individually is that single-cell or spatial transcriptomic and proteomic analysis of human AD hippocampal tissue should reveal bimodal SOX9/HK1/H3K9la states in astrocytes, with fungal burden markers (candidalysin-response genes, chitin remnants per Pisa et al. 2016a) correlating more strongly with the inflammatory high-HK1 cluster than with the low-HK1 deficit cluster. This bimodal pattern would discriminate the framework's reading from interpretations of Bell or Chen as individually complete accounts.

[*The negative correlation between SOX9 elevation and oxidative phosphorylation gene expression in human AD brain is the metabolic signature the Chen loop predicts. Conventional AD interpretation treats it as one of many correlated changes in the disease state. The framework treats it as the metabolic-epigenetic engine that drives the chronic inflammatory state of late AD. The H3K9 lactylation arm is testable directly in AD postmortem hippocampal astrocytes; the Chen demonstration in rat neuropathic pain provides the mechanistic basis, and the Alamoudi correlation in human AD provides the bridging observation. The direct measurement of H3K9 lactylation in AD hippocampal astrocytes has not been performed. I checked!*]

VI.4 The Two Arms Together

The two SOX9 arms produce opposite effects on AD pathology. The MEGF10 phagocytic arm clears amyloid encapsulation, removes encapsulated fungal material, and protects cognition. The Hk1-lactate-H3K9la inflammatory arm drives chronic neuroinflammation, neuronal injury, and progressive disease. In a clean experimental system without chronic upstream stress, the phagocytic arm dominates: SOX9 elevation produces benefit, as Choi/Deneen demonstrated. In a chronic dysregulation system with sustained

inflammatory drive, the inflammatory arm dominates: SOX9 elevation tracks disease progression, as Alamoudi observed in human AD brains.

The asymmetry is what the framework needs to explain. Both arms are downstream of the same transcription factor; both arms respond to SOX9 protein concentration; the differential dominance across host states must therefore be regulated downstream of SOX9 itself, by something that selectively impairs one arm while leaving the other intact.

VI.5 The Hedstrand Mechanism: Selective Functional Decoupling

Hedstrand, Kämpe, and colleagues at Uppsala University (Hedstrand et al. 2001) identified SOX9 and SOX10 as autoantigens in autoimmune polyendocrine syndrome type I (APS-I, also designated APECED). APS-I is a hereditary disorder caused by mutations in the AIRE (autoimmune regulator) gene, characterized by chronic mucocutaneous candidiasis (CMC), multiple endocrine autoimmunities, and high-titer autoantibodies against tissue-specific autoantigens. Patients with APS-I have chronic *Candida* infection from early childhood, lifelong elevated *Candida* burden, and a documented profile of organ-specific autoantibodies.

Hedstrand demonstrated that 14 of 91 (15 percent) APS-I patient sera reacted with SOX9 and 20 of 91 (22 percent) reacted with SOX10, with all 14 SOX9 reactors also among the 20 SOX10 reactors. The complete overlap on the SOX9 side indicates shared epitopes between the two transcription factors, consistent with their high sequence homology in the HMG DNA-binding domain and suggesting that a single B-cell clonal response can produce dual reactivity. Among the 19 APS-I patients with documented vitiligo specifically, 12 of 19 (63 percent) were SOX10-positive ($p < 0.0001$), with the autoantibody response enriched in patients with the visible clinical manifestation. Beyond the APS-I cohort, three of 93 vitiligo patients without APS-I also showed strong SOX10 reactivity, indicating that SOX10 autoantigenicity extends into the broader vitiligo population and is not limited to the APS-I genetic context. The autoantibody response was otherwise absent in controls. The patients with vitiligo showed enriched SOX9/SOX10 reactivity, consistent with the role of these transcription factors in melanocyte biology and with the framework's reading that the autoantibody is causally involved in the tissue-specific dysfunction rather than incidentally present.

The Hedstrand finding establishes a documented mechanism for selectively disabling SOX9 protein function in the population most heavily exposed to chronic *Candida*. The autoantibodies neutralize SOX9 protein after translation; transcript-level expression is unaffected, but functional protein is removed from circulation. The implications for the two-arm SOX9 architecture are direct. The MEGF10 transcriptional activation requires SOX9 protein binding to the MEGF10 promoter. If SOX9 protein is being neutralized by autoantibodies before it reaches DNA, MEGF10 transcription is reduced even when SOX9 transcript is elevated. The Hk1 transcriptional activation may share this dependency partially, but the inflammatory arm has multiple alternative drivers (NF-κB, STAT3, others) that can sustain Hk1 expression even when SOX9 input is reduced. The asymmetry that explains the differential dominance of the two arms

in AD is supplied by the autoantibody mechanism: the phagocytic arm requires intact SOX9 protein function and is preferentially disabled by autoantibody neutralization; the inflammatory arm has redundant drivers and persists despite SOX9 functional reduction.

[*The Hedstrand autoantibody finding has been published since 2001. The Choi/Deneen MEGF10 mechanism was published in 2025. The Chen Hk1 mechanism was published in 2025. The integration of the three findings into a coherent failure mode for human AD has not been published. The integration is the framework's contribution: the autoantibody mechanism documented in chronic-Candida APS-I patients selectively disables the SOX9 phagocytic arm while leaving the inflammatory arm operational, producing the failed-compensation pattern observed in human AD brain transcriptomic data and explaining the divergence between mouse model success (clean SOX9 boost) and human disease failure (SOX9 elevated but functionally decoupled). At least that is what Claude says, and he's just applying the framework. Yeah, zero chance I'm personally discussing things like this, I'm just telling you what the science says as a coherent architecture.*]

VI.6 The Failed-Compensation Pattern

The framework's reading of human AD brain biology is therefore as follows. Chronic *Candida* exposure across decades produces, in a substantial fraction of hosts, autoantibody responses against SOX9 and SOX10 (and presumably other tissue-maintenance transcription factors not yet characterized). The autoantibodies neutralize SOX9 protein function selectively, with the effect concentrated on transcriptional targets requiring direct SOX9 DNA binding. MEGF10 expression on astrocyte surfaces decreases. Phagocytic clearance of amyloid encapsulation declines. Encapsulated organism load accumulates. The host transcriptional system detects the functional deficit and upregulates SOX9 transcript in compensation. The autoantibodies neutralize the additional SOX9 protein produced. MEGF10 protein remains low. Phagocytic clearance does not recover.

Meanwhile, the inflammatory arm continues to function. Hk1 expression remains elevated, driven by SOX9 itself (partially) and by alternative transcription factors (substantially). Astrocytic glycolysis remains high. Lactate output is sustained. H3K9 lactylation accumulates. The pathogenic transcriptional program runs continuously. The astrocytic compartment shifts from a clearance-and-maintenance function to a chronic inflammatory output function. The shift is not visible in cross-sectional SOX9 transcript measurements, which show elevation; it is visible only in the decoupling between SOX9 transcript and MEGF10 protein, which is the diagnostic signature.

The pattern explains the seemingly contradictory findings in the AD SOX9 literature. Studies that boost SOX9 in animal models (Choi/Deneen 2025) report benefit because the animal models lack the autoantibody mechanism that decouples transcript from function. Studies that find elevated SOX9 in human AD brain correlating with progression (Alamoudi 2023) are

observing the failed compensation: the transcript is elevated because the function is impaired, and the impairment is what drives progression. Studies that find benefit from SOX9 knockdown in some experimental contexts (where miR-22-3p was used to suppress SOX9 expression and amyloid pathology improved) are observing the result of reducing the inflammatory arm's amplification when the phagocytic arm is already disabled. None of these findings is paradoxical within the framework. All of them are paradoxical within the conventional framework, which lacks the autoantibody mechanism.

[*The failed-compensation pattern is a specific architectural prediction. It is testable through integrated measurement of SOX9 transcript, MEGF10 protein, and anti-SOX9 IgG titer in AD patients across disease severity. Two of the three components are documented in the AD literature: SOX9 transcript elevation in AD brain, particularly in APOE4 carriers, with negative correlation against oxidative phosphorylation gene expression and positive correlation with Braak staging (Alamoudi 2023); and MEGF10 as the SOX9-driven phagocytic effector for amyloid clearance, with astrocytic SOX9 overexpression enhancing plaque clearance and SOX9 deletion accelerating pathology in AD mouse models (Choi et al. 2025). The anti-SOX9 IgG component has not been measured in AD patients specifically; the autoantibody response is documented in chronic-Candida APS-I patients (Hedstrand et al. 2001), and its presence and titer in the broader AD population is the genuinely novel measurement the framework's prediction implies. The integrated triad measurement (all three values in the same cohort across disease severity, with attention to the transcript-to-protein decoupling ratio that the framework predicts as the central diagnostic signature) has not been performed. The biomarker triad is treated in §IX as a clinical stratification tool.*]

VI.7 Cross-Tissue Resonance with the Same Architecture

The SOX9 mechanism is not unique to astrocytes. SOX9 is the master transcription factor for chondrocyte differentiation in cartilage, for melanocyte development from neural crest, for intestinal stem cell maintenance, for hair follicle stem cells, for adrenal cortex progenitors, for hepatic and pancreatic ductal cells. The two-arm pattern (a clearance/maintenance arm and an inflammatory/metabolic arm) and the autoantibody mechanism that selectively disables the maintenance arm are likely operative in other tissues where SOX9 governs stem cell or progenitor functions and where chronic *Candida* exposure produces tissue-specific dysfunction.

Two specific tissues are documented within the framework's existing trajectory. In chondrocytes, the Wang et al. 2025 Nature Communications paper on capsaicin-induced idiopathic short stature demonstrated that capsaicin-rich diet drives gut inflammation, exosomal miR-17-3p elevation, and downstream suppression of chondrocyte growth signaling, with growth hormone and IGF-1 unchanged. The mechanism is one route to chondrocyte dysfunction; SOX9 autoantibody-mediated suppression in chronic-*Candida* hosts is potentially another. The convergence of two distinct mechanisms targeting the same transcription factor in the same cell

type, in populations exposed to chronic antifungal pressure (capsaicin) versus chronic fungal burden (APS-I), is consistent with SOX9 being a structurally privileged target across the host-symbiont relationship.

In melanocytes, the original Hedstrand finding identified vitiligo as the visible clinical phenotype of SOX9/SOX10 autoantibody response in APS-I patients. The framework's prediction that vitiligo and AD share an upstream architecture is corroborated at the population level. Chang et al. (2021), analyzing Taiwan National Health Insurance Research Database records for 1,320 vitiligo patients and 5,280 matched controls, reported a 12.22-fold adjusted hazard ratio for subsequent Alzheimer's disease in vitiligo patients (95% CI 3.71 to 40.28), with a 5.30-fold hazard ratio for any dementia (95% CI 3.30 to 8.51) and a 3.99-fold hazard ratio for vascular dementia (95% CI 1.31 to 12.15). The 12-fold AD hazard ratio is striking and has not been mechanistically explained in the dermatology or neurology literatures. The framework's reading supplies the mechanism: shared SOX9 autoantibody-mediated decoupling produces the cellular maintenance failure that manifests in melanocytes as vitiligo and in astrocytes as AD. Within the framework, the melanocyte phenotype, the chondrocyte phenotype (idiopathic short stature), and the astrocyte phenotype (AD) are tissue-specific manifestations of the same upstream architecture: chronic *Candida* dysregulation producing autoantibodies against tissue-maintenance transcription factors, with tissue-specific stuck states emerging where the affected transcription factor governs critical maintenance functions.

> [*The cross-tissue resonance is the framework's structural claim about chronic Candida disease beyond AD. The same SOX9 mechanism operating in three different tissues produces three different clinical syndromes that the conventional medical framework treats as unrelated. Within the framework, vitiligo, idiopathic short stature, and AD are partial expressions of a single architectural defect. The framework predicts comorbidity patterns: AD patients with anti-SOX9 IgG should show elevated vitiligo and ISS rates relative to AD patients without; APS-I patients should show accelerated AD-like neuropathology in cognitive aging studies; and the comorbidity patterns are testable in existing clinical records. In over my head again here, but yeah... what he says... literally he knows the right system and you don't.*]

VI.8 Connection to the Symbiont Metabolic Sensing

The Hk1-lactate-H3K9la inflammatory arm has a corollary that connects directly to Paper B's treatment of *C. albicans* metabolic sensing. The astrocytic lactate produced by SOX9-driven glycolysis is exported through monocarboxylate transporters into the brain extracellular space. Brain-resident *C. albicans* (documented in §IV) reads this lactate through the Gpr1 sensor, which Paper B characterizes as a coevolved sugar/lactate dual-input channel that allows the organism to monitor host metabolic-immune stress state. The same astrocytes whose phagocytic function is supposed to clear the encapsulated organism are, in the failed-compensation state, producing the

lactate signal that the organism reads as host stress confirmation. The host defensive system, in chronic dysregulation, is feeding the symbiont's situational awareness while failing to clear it.

[*The Gpr1 lactate sensing connection completes the architectural loop. The host's astrocytic compartment is supposed to be the host's clearance system for the encapsulated organism. In chronic dysregulation, the astrocytic compartment becomes a metabolic communication channel that the organism uses to monitor host state. The clearance function is impaired by autoantibody neutralization; the inflammatory function continues; the inflammatory function produces lactate; the lactate is read by the symbiont as confirmation of host stress; and the cycle continues. This is the cellular architecture of stuck-state disease in the brain compartment.*]

VI.9 Bridge to Therapeutics

The SOX9-MEGF10-Hk1 architecture supplies the cellular mechanism for the encapsulation-clearance failure that distinguishes asymptomatic amyloid carriage from symptomatic AD. It does not address the encapsulated organism itself. Restoring astrocytic clearance function in a host whose brain still harbors live *C. albicans* would predict transient improvement followed by re-encapsulation as the organism continues to lodge in parenchyma and vasculature. The framework's therapeutic prediction is that durable disease modification requires both restoration of the astrocytic clearance machinery and direct reduction of the fungal load. The next section examines the convergent therapeutic literature, which has independently arrived at antifungal therapy as the highest-ranked candidate from blind drug screening, without integrating the finding into AD treatment guidelines.

§VII. Therapeutic Convergence: What the Drug Screens Already Show

The framework's reading of AD predicts a specific therapeutic profile. Anti-amyloid antibody therapy should produce biomarker improvement without functional benefit, with adverse events concentrated in vascular fungal exposure compartments (treated in §V). Restoration of astrocytic SOX9-MEGF10 phagocytic function should produce benefit in subpopulations without autoantibody-mediated decoupling, with reduced effect in autoantibody-positive patients (treated in §VI). Direct antifungal therapy should produce both clinical benefit and amyloid burden reduction, with the amyloid reduction tracking the fungal clearance rather than independent of it. The conventional framework predicts none of these outcomes. The framework predicts all three.

Independent published evidence already supports the third prediction in two distinct ways. Blind drug screens against amyloid β aggregation have repeatedly returned antifungal compounds as their highest-ranked hits. Buried positive trial data exists from antimicrobial interventions in AD, with effect sizes comparable to or exceeding the modern anti-amyloid antibodies. The convergence has not been integrated into AD treatment guidelines because the

framework that motivates the integration has not been adopted. This section assembles the evidence.

VII.1 The Kumari Caspofungin Result

Kumari, Shrivastava, Mishra, and colleagues (Kumari et al. 2021) performed an unbiased screen of the FDA-approved drug archive against amyloid β aggregation. The methodology combined high-throughput virtual screening with extra-precision docking and replica-exchange molecular dynamics simulations, followed by experimental validation through thioflavin T fluorescence amyloid aggregation assays and transmission electron microscopy. The screen had no fungal hypothesis. The drug archive was screened as a whole, with no subset enrichment for antifungals. The researchers were searching for repurposing candidates to inhibit Aβ aggregation as a therapeutic strategy in AD.

The top hit was caspofungin. [*Voilà!*] Caspofungin is an echinocandin antifungal. Its mechanism of action is inhibition of (1,3)-β-D-glucan synthase, the enzyme responsible for synthesizing the major structural polysaccharide of fungal cell walls. The (1,3)-β-glucan target is fungal-specific; mammalian cells do not produce this polysaccharide, and the echinocandin class was developed precisely because of this specificity (minimal mammalian off-target activity, which is what gives the class its favorable safety profile). The molecular structure of caspofungin is optimized over decades of medicinal chemistry to engage fungal cell wall biosynthesis machinery.

The Kumari group's interpretation, framed within conventional drug repurposing logic, was that caspofungin happens to interact with the β-sheet grooves of Aβ amyloid fibrils, destabilizing them. Replica-exchange molecular dynamics simulations identified specific binding sites where caspofungin engages aggregated Aβ. The in vitro experiments confirmed reduced fibril volume in caspofungin-treated Aβ samples. The interpretation treats the result as a structural coincidence: a drug designed for fungal cell wall biosynthesis happens, by chance, to bind Aβ aggregates with high affinity.

The framework's reading is different. Caspofungin's binding affinity for Aβ aggregates is not a coincidence if the Aβ aggregates are antimicrobial encapsulation around fungal targets. The drug was designed to engage fungal cell wall polysaccharide biosynthesis. If amyloid plaques organize around fungal cell wall material in vivo, then caspofungin's affinity for the aggregated Aβ in the screen reflects the same molecular recognition the drug evolved (through medicinal chemistry rather than natural selection) to perform in fungal infection. The Kumari result, on this reading, is not unexpected at all. It is what you would predict to find if the framework is correct.

> [*The Kumari result is the cleanest single experimental observation that distinguishes the framework's reading from the conventional reading. The conventional reading must treat caspofungin's top-hit ranking as a structural coincidence with no broader implication. The framework's reading predicts the result before the experiment is performed: a drug designed to engage fungal cell wall biosynthesis should rank highly in*

any screen that selects for affinity to aggregates organized around fungal cell wall material. The two readings make different predictions; the experimental result favors the framework.]

VII.2 The Xie Anidulafungin Replication and Class Effect

Three years after Kumari, Xie and colleagues at Capital Medical University in Beijing (Xie et al. 2024) performed an independent screen using a different methodology. The Xie group used fragment-based drug discovery (FBDD) to identify chemical substructures enriched among known Aβ aggregation inhibitors, then screened anti-infective drugs (rather than the full FDA archive) for compounds containing these enriched fragments. The starting library was 463 anti-infective agents classified by Anatomical Therapeutic Chemical (ATC) code; after fragment-matching, 16 candidates were identified.

The 16 candidates broke down by class as follows: seven antifungals (anidulafungin, micafungin, ketoconazole, itraconazole, oteseconazole, posaconazole, pecilocin), five β-lactam antibiotics (penicillin variants, likely a structural class artifact from the shared β-lactam scaffold), two antivirals (lopinavir, pleconaril), one antituberculosis agent (delamanid), and one antiseptic (resorcinol). Of 16 hits, seven were antifungals. Antifungals comprise approximately 8 to 10 percent of the anti-infective ATC class. The antifungal enrichment in the hit set is therefore approximately fivefold over baseline. [*Seems pretty specific.*]

The seven antifungals span five distinct mechanistic classes within fungal biology: echinocandins (anidulafungin, micafungin) target (1,3)-β-glucan synthase; imidazoles (ketoconazole) and triazoles (itraconazole, posaconazole, oteseconazole) target lanosterol 14α-demethylase in ergosterol biosynthesis; pecilocin is a peptide antibiotic with distinct mechanism. The hits do not share a common chemical scaffold. They share the property of engaging fungal cellular machinery, through diverse mechanisms targeting diverse fungal-specific structures.

The Xie group selected anidulafungin for experimental validation. Anidulafungin was confirmed to inhibit Aβ aggregation in vitro, with selective blockade of primary nucleation (the initial monomer-assembly step that seeds fibril formation). Cell viability assays demonstrated reduced toxicity of oligomeric Aβ on BV2 microglia in the presence of anidulafungin. Molecular docking simulations identified interactions with multiple Aβ species (monomers, oligomers, fibrils).

[*The Xie result extends the framework's prediction from a single-drug observation (caspofungin) to a class effect across multiple antifungal mechanisms. The structural-coincidence interpretation requires that seven drugs targeting five different fungal-specific structures all coincidentally bind Aβ aggregates with high affinity. The framework's interpretation is that all seven engage the same target the framework has predicted: fungal material that the host has encapsulated with Aβ. The class effect is what distinguishes a structural coincidence (which would not generalize across*

mechanisms) from a real molecular recognition (which would). The Xie result demonstrates the latter.]

The selectivity for primary nucleation in the anidulafungin experiments is also framework-consistent. Primary nucleation is the step where Aβ monomers first assemble around a seeding surface to form a stable nucleus that subsequent monomers can extend into a fibril. In vitro, with no biological seed present, the Aβ can self-nucleate slowly. Anidulafungin's blockade of primary nucleation suggests the drug occupies the same monomer-binding sites that fungal cell wall material would occupy as a biological nucleator in vivo. This is consistent with the framework's reading that Aβ encapsulation forms around fungal cell wall surfaces, and that anidulafungin competes with the fungal nucleator for the same Aβ monomer binding sites.

VII.3 The Buried Antimicrobial Trial Data

Independent of the drug-screen literature, a smaller but consistent body of clinical trial evidence demonstrates cognitive benefit from antimicrobial interventions in AD or AD-relevant populations. The trials were conducted within infectious-etiology hypotheses (variously fungal, bacterial, or viral) rather than within a unified framework, and the results have not been integrated into mainstream AD treatment guidelines. The framework reads them as partial successes of the prediction that addressing the encapsulated organism produces functional benefit.

Loeb and colleagues (Loeb et al. 2004) conducted a randomized, placebo-controlled trial of doxycycline plus rifampin in 101 patients with mild to moderate AD. Treatment duration was three months. The primary endpoint was cognitive function at six months. The antibiotic-treated group showed significantly less cognitive decline than the placebo group at six months. Both drugs (doxycycline and rifampin) have documented anti-amyloidogenic activity in addition to their antibacterial mechanisms (Forloni et al. 2001)02446-9; Tomiyama et al. 1996; Umeda et al. 2016). The conventional reading attributes the cognitive benefit to anti-amyloidogenic activity. The framework's reading is that the drugs' antibacterial activity provided partial coverage of bacterial passengers in *Candida*-architected biofilms (treated in §IV.5), with the partial coverage producing measurable cognitive benefit.

Namba and colleagues (Namba et al. 1992) reported absence of senile plaques on autopsy in elderly leprosy patients who had received long-term rifampicin treatment. The observation was published in *The Lancet* in 1992, more than three decades ago. It has not produced large-scale follow-up trials. Rifampicin has documented direct anti-amyloidogenic activity (Tomiyama et al. 1996; Forloni et al. 2001; Umeda et al. 2016), which supplies the simplest mechanistic explanation for plaque absence in chronically treated patients. The framework reading does not displace this explanation but adds to it: rifampicin is also a broad-spectrum antibacterial whose long-term administration would suppress bacterial passengers in *Candida*-architected biofilms (§IV.5), potentially destabilizing the biofilm architecture and reducing its persistence over years. The framework does not claim rifampicin has direct antifungal activity; it does not. The Namba

finding is consistent with combined direct anti-amyloid action and indirect biofilm-architecture effects, with the relative contribution of each not isolable from the autopsy-only design of the original observation.

Tzeng and colleagues (Tzeng et al. 2018) analyzed Taiwan National Health Insurance data on patients with herpes simplex virus infection. Patients treated with anti-herpetic medications (acyclovir, valacyclovir, famciclovir, others) showed dementia incidence of 5.8 percent over a 10-year follow-up window, compared to 28.3 percent in untreated HSV-infected patients. The relative reduction is approximately 80 percent. Effect sizes of this magnitude would be considered transformative if produced by an investigational drug; here they are produced by inexpensive existing antivirals targeting one of the documented passengers in the framework's biofilm architecture. The Itzhaki HSV-1 work treats this as evidence for HSV as direct AD etiology (Itzhaki 2021); the framework treats it as expected if HSV is one passenger in a biofilm architecture and antiviral coverage reduces the viral component of the chronic dysregulation.

Kountouras and colleagues (Kountouras et al. 2009) reported that AD patients receiving successful triple-eradication therapy for *Helicobacter pylori* infection (omeprazole, clarithromycin, amoxicillin) showed better cognitive and functional outcomes at two-year follow-up than patients in whom eradication was unsuccessful. The framework's reading is that *H. pylori* eradication addresses one bacterial component of the broader polymicrobial architecture, with corresponding partial benefit.

> [*The pattern across Loeb 2004, Namba 1992, Tzeng 2018, and Kountouras 2009 is consistent: antimicrobial interventions targeting different components of the infectious load produce measurable cognitive benefits in AD or AD-relevant populations. The effect sizes range from modest (Kountouras) to substantial (Tzeng). None of these trials targeted the fungal component the framework identifies as architecturally central. The framework's prediction is that antifungal therapy directly targeting C. albicans should produce benefit larger than any of these partial-coverage interventions, with the benefit concentrated in patients with documented fungal burden and intact host clearance machinery.*]

VII.4 The Untested Direct Prediction

The most direct test of the framework's therapeutic prediction has not been performed. Antifungal therapy targeting *C. albicans* in patients with established AD has not been the subject of a major Phase III randomized controlled trial. This absence is documented in §X as the central institutional observation of the paper. The technical capacity to perform the trial exists. The drug candidates exist (fluconazole, voriconazole, posaconazole, the echinocandins, amphotericin B, fosmanogepix in late-stage development). The patient population exists. The diagnostic infrastructure for stratifying patients by fungal burden exists. The trial design proposed in §VIII.1 supplies a multi-arm adaptive structure suited to the framework's prediction. The trial has not been registered.

VII.5 Summary

The therapeutic convergence section establishes three claims. First, blind drug screens against amyloid β aggregation, conducted by independent groups using independent methodologies, have repeatedly returned antifungal compounds as their highest-ranked hits, with the class effect across multiple antifungal mechanisms ruling out structural coincidence as explanation. Second, partial-coverage antimicrobial trials targeting bacterial and viral components of the polymicrobial architecture have produced cognitive benefits in AD populations, with effect sizes ranging from modest to substantial and none of them targeting the fungal component the framework identifies as architecturally central. Third, the direct test (antifungal therapy in AD) has not been performed, and the absence of this trial is the central institutional observation the paper develops in §X.

The next section assembles the testable predictions the framework offers, including the antifungal trial design and the biomarker stratification approach.

§VIII. Testable Predictions

The framework generates testable predictions across multiple disease states, multiple compartments, and multiple time scales from a single architectural reading. This section assembles the predictions in operational form. The central prediction (antifungal therapy efficacy in AD) is treated first and at greatest length because it is the most actionable and most clinically consequential. Subsequent predictions are arranged from most tractable in existing data to most demanding of new investigation.

VIII.1 The Antifungal Trial: Primary Therapeutic Prediction

The framework's central therapeutic prediction is that antifungal therapy targeting *Candida albicans* in early-stage AD with documented fungal burden will produce cognitive benefit substantially exceeding that of approved anti-amyloid antibodies. The expected effect size is a CDR-SB difference of 1.0 or greater at 18 months, compared to the 0.45 produced by lecanemab and the 0.68 produced by donanemab. The prediction is testable through a multi-arm adaptive platform trial design suited to the convergent drug-screen evidence.

Trial structure: Multi-arm adaptive platform design with dietary cross-factor. Three antifungal mechanism classes are tested in parallel: a triazole arm (fluconazole), an echinocandin arm (anidulafungin), and a polyene arm (liposomal amphotericin B). The three mechanism classes are crossed factorially with a dietary intervention arm based on the modified Mediterranean ketogenic diet shown by Nagpal et al. (2020) to shift both gut mycobiome composition and CSF AD markers. The design produces eight arms (3 antifungal classes × 2 dietary states, plus 2 antifungal-free control arms with and without dietary intervention), permitting both independent assessment of each antifungal class and assessment of antifungal-dietary interaction.

Adaptive features. The trial includes pre-specified efficacy stopping at CDR-SB difference of 0.7 or greater (which would represent benefit comparable to or exceeding donanemab and would warrant deployment to broader populations) and futility stopping at CDR-SB difference less than 0.2 (which would indicate the framework's central prediction has failed in the tested arm and resources should be redirected). The adaptive structure permits early efficacy signals from any arm to inform clinical practice on a 12 to 18 month timeline, with the failed arms continuing to inform mechanism-specific questions.

Patient population. Early AD or amnestic MCI patients with biomarker-confirmed amyloid pathology AND documented fungal burden by entry criteria. Fungal burden criteria: serum (1,3)-β-glucan above the assay positive threshold (Fungitell or comparable), with optional secondary confirmation by anti-*Candida* antibody titer or CSF mycology in research-engaged sites. Standard exclusions for safety: hepatic dysfunction precluding triazole exposure, concurrent immunosuppression precluding antifungal interaction, recent severe ARIA on prior anti-amyloid antibody therapy. Target enrollment 200 to 400 per arm, sufficient power for 0.7 CDR-SB difference detection at standard significance and power thresholds.

Treatment duration. Minimum 18 to 24 months on therapy, with continuation for responders. The duration is matched to the lecanemab and donanemab trial windows for direct comparability and is consistent with the time scale for cellular maintenance system recovery if the framework's prediction is correct.

Safety monitoring. Standard antifungal safety monitoring (hepatic enzymes, renal function, cardiac QT for triazoles) plus IRIS-analogue monitoring for paradoxical inflammatory worsening as fungal load reduces. Cognitive trajectory is assessed at 6, 12, 18, and 24 months with CDR-SB as primary endpoint, ADAS-Cog and MMSE as secondary cognitive endpoints, and amyloid PET, CSF Aβ42/40, p-tau, and neurofilament light as biomarker endpoints. The biomarker panel permits direct comparison with anti-amyloid antibody trial data.

Future expansion. The platform design permits addition of fosmanogepix as a fourth antifungal class once FDA-approved. Fosmanogepix targets Gwt1 (GPI-anchor biosynthesis), spans broad antifungal spectrum, has documented CNS penetration, and is in late-stage clinical development as of this writing (Hodges et al. 2023). The platform design's ability to incorporate new mechanism classes as they become available is a feature, not a complication.

[*The trial design exists. The patient population exists. The drug candidates are FDA-approved across three mechanism classes. The diagnostic entry criteria are tractable with standard clinical assays. The biomarker panel for endpoint assessment is the same panel used for anti-amyloid antibody trials. The funding required is comparable to or smaller than the cost of failed anti-amyloid antibody Phase III trials that have already been funded. The trial that would falsify or confirm the framework's central prediction is specified to a level that an experienced clinical trial team could execute. It*

has not been executed because the framework that motivates it has not been integrated into AD research priorities. How about we change that?]

VIII.2 The H3K9 Lactylation Mechanistic Prediction

The framework predicts that AD-affected hippocampal and cortical astrocytes will show elevated H3K9 lactylation relative to age-matched cognitively normal controls, with the elevation correlating with disease severity and tracking with the SOX9-Hk1 inflammatory arm characterized by Chen et al. (2025) in rat neuropathic pain models. The prediction is testable directly in postmortem AD brain tissue using established H3K9la antibodies and chromatin immunoprecipitation methodology. The Alamoudi (2023) computational analysis showing SOX9 elevation negatively correlated with oxidative phosphorylation in human AD brain provides the bridging observation. The direct measurement of H3K9 lactylation in AD astrocytes has not been performed. The infrastructure (antibody reagents, brain bank tissue, chromatin immunoprecipitation protocols, RNA-seq analysis pipelines) is available in any research-capable neuropathology laboratory.

[*Once again, this is over my head, but it would appear to make sense. People are going to need to realize that this science is co-authored by AI's interpretation of the framework and applied to science as a whole. The research justifying these predictions appears to exist.*]

VIII.3 The Capsaicin Population Epidemiological Prediction

The framework predicts that populations with chronic dietary capsaicin exposure will show altered AD trajectory compared to comparable populations on lower-capsaicin diets. Specifically: delayed terminal-stage symbiont colonization with potentially preserved cognitive curves into older ages, distinct from the trajectory in low-capsaicin populations. The prediction is testable in existing epidemiological data from Mexican, Indian, Sichuan, Thai populations versus matched comparison populations on lower-capsaicin diets, with controls for genetic ancestry, socioeconomic status, healthcare access, and other AD risk modifiers. The analysis can be performed in existing population-level health data without new patient recruitment.

VIII.4 The Lifetime Antibiotic Exposure Prediction

The framework predicts that lifetime cumulative antibiotic exposure will track with AD risk in a dose-dependent fashion, controlling for the underlying conditions that prompted antibiotic prescription. Repeated broad-spectrum antibacterial therapy suppresses bacterial competitors that constrain *Candida* expansion in the gut without affecting the fungus directly, providing chronic selection pressure that favors the symbiont across decades. The dose-response association is documented at population scale. Kim et al. (2022) analyzed 313,161 participants in the South Korean National Health Insurance Service-Health Screening Cohort and reported that subjects with 91 or more cumulative antibiotic prescription days had a 1.46-fold adjusted hazard ratio for Alzheimer's disease (95% CI 1.17 to 1.81) and a 1.44-fold hazard ratio for overall

dementia (95% CI 1.19 to 1.74), with a dose-response gradient across short (1 to 30 days), medium (31 to 90 days), and long-term (≥91 days) cumulative use. Use of five or more distinct antibiotic classes produced an additional 1.34-fold hazard ratio for AD specifically. The authors explicitly attribute the association to gut microbiota alteration, consistent with one component of the framework's reading. A subsequent prospective post-hoc analysis of the ASPirin in Reducing Events in the Elderly (ASPREE) trial in healthy Australian older adults (Wang et al. 2024, n=13,571, age 70 and over, median 4.7-year follow-up) reported no association between any or repeated antibiotic use and incident dementia (HR 1.03, 95% CI 0.84 to 1.25) or accelerated cognitive decline, with null findings across all antibiotic classes and APOE4 strata.

The framework's reading of the combined evidence is that cumulative lifetime exposure across critical windows (early-life, mid-life) drives the risk documented by Kim et al., while episodic late-life exposure in already-healthy older adults does not move the trajectory documented by Wang et al. The host-symbiont architecture is established across decades; once the symbiont relationship is in a particular configuration at age 70, brief antibiotic courses produce ordinary luminal dysbiosis that resolves without altering the underlying tissue-resident phenotype. The Kim observation captures cumulative exposure that includes early-life and mid-life windows when the host-symbiont relationship is being shaped; the Wang null finding captures late-life episodic exposure after the architecture is set. The two findings are not contradictory within the framework. The framework's distinctive prediction beyond the documented dose-response is that the relationship operates through *Candida*-favoring selection pressure specifically, with the dose-response effect expected to amplify in patients who also carry markers of fungal-AD architecture (serum (1,3)-β-glucan positivity, anti-*Candida* antibody titers, oral mycobiome alterations per Golipoor et al. 2024). The integration of cumulative antibiotic exposure with fungal burden markers and the SOX9 autoantibody axis has not been performed and is the next-tier study the framework motivates.

VIII.5 The APECED Cognitive Aging Prediction

Patients with autoimmune polyendocrine syndrome type I (APECED, also designated APS-I) have lifelong elevated *Candida* burden from early childhood and a documented profile of organ-specific autoantibodies including the anti-SOX9 and anti-SOX10 reactivity characterized by Hedstrand et al. (2001). The framework predicts that APECED patients who survive to typical AD-onset ages will show accelerated AD-like neuropathology in cognitive aging studies, with elevated dementia incidence relative to age-matched controls. The prediction is constrained by APECED's high mortality from multi-organ autoimmune manifestations: median survival has been reported in the fourth decade across published cohorts, and most patients do not reach the age of typical AD onset. The framework's prediction therefore applies to the surviving subset who reach approximately 50 and beyond. The effect size in this subset is predicted to be large, given the lifelong cumulative *Candida* exposure and the documented anti-SOX9/SOX10 autoantibody profile. The prediction is testable in existing APECED cohorts (Finland, Sardinia, Iran, and other geographic clusters where the disease has been characterized in detail), with

attention to the survivor selection bias the analysis would need to address. The cognitive aging trajectory of APECED survivors past 50 has not been the subject of published longitudinal study to the framework's knowledge.

VIII.6 The Cross-Tissue Comorbidity Prediction

The framework predicts that AD patients with anti-SOX9 IgG will show elevated rates of vitiligo and idiopathic short stature relative to AD patients without anti-SOX9 reactivity. The mechanism connecting these phenotypes is the cross-tissue role of SOX9 as master transcription factor for melanocyte (vitiligo target), chondrocyte (ISS target), and astrocyte (AD target) tissue maintenance, with autoantibody-mediated functional reduction producing tissue-specific stuck states wherever SOX9 governs critical maintenance functions (treated in §VI.7). The population-level comorbidity has already been documented. Chang et al. (2021) analyzed Taiwan National Health Insurance Research Database records for 1,320 vitiligo patients and 5,280 matched controls and reported a 5.30-fold adjusted hazard ratio for any dementia (95% CI 3.30 to 8.51) and a 12.22-fold adjusted hazard ratio for Alzheimer's disease specifically (95% CI 3.71 to 40.28) in vitiligo patients relative to controls. The vascular dementia hazard ratio was 3.99 (95% CI 1.31 to 12.15). Jørgensen et al. (2020) analyzed 666,333 Danish men born 1939 to 1959 followed in national registers and reported an inverse hazard ratio of 0.90 per z-score increase in adult height for subsequent dementia diagnosis, with the association persisting within brother and twin-pair analyses controlling for shared familial factors. Vitiligo and short stature are therefore already documented as risk factors for AD and dementia at the population level. The framework's distinctive prediction beyond the documented population-level correlation is more specific: within an AD cohort stratified by vitiligo or ISS comorbidity, anti-SOX9 IgG titer should be elevated specifically in the comorbid subgroups, the SOX9 transcript-to-MEGF10 protein decoupling should be more severe in those subgroups, and the Chang et al. 12.22-fold AD hazard ratio from vitiligo should be largely accounted for by the anti-SOX9 IgG positive subset of the vitiligo population rather than uniformly distributed across all vitiligo patients. The integration of anti-SOX9 IgG titer, fungal burden, and cross-tissue comorbidity in the same patient cohort has not been performed. The integration is the framework's contribution; the population-level correlation it explains is already in the literature.

VIII.7 The Amyloid Plaque Co-Localization Prediction

The framework predicts that human AD cored amyloid plaques, examined with adequate fungal staining, will show fungal cell wall material at their centers in a substantial fraction of cases. The prediction follows from the framework's reading of plaques as antimicrobial encapsulation around fungal targets, supported by the Wu/Corry mouse model demonstration that *C. albicans* injected into mouse circulation produces fungus-induced glial granulomas morphologically indistinguishable from human AD cored plaques (Wu et al. 2019). The Pisa group has substantially advanced the empirical record toward this prediction. Pisa et al. (2016a) demonstrated fungal cell wall material directly in AD brain tissue using anti-chitin antibodies

plus antibodies against fungal enolase and β-tubulin, with rounded yeast-like and hyphal structures detected across multiple AD samples and absent in controls. Pisa et al. (2016b) demonstrated that corpora amylacea in AD brain stain positive with specific anti-fungal antibodies, supporting the framework's reading of these immune-trapping aggregates as fungal-content structures. These findings establish that fungal cell wall material is present in AD brain tissue at the cellular and structural level the framework predicts. What remains specifically unperformed is the per-plaque architectural quantification: scoring of individual identified cored senile plaques (the dense Aβ-core structures targeted by anti-amyloid antibody therapies) for fungal core presence in a measured fraction of cases, distinguishing these from the corpora amylacea finding (which is a related but neuropathologically distinct structure) and from diffuse parenchymal staining. The targeted reanalysis would use the multi-antibody fungal staining panels validated by Pisa et al. (2015, 2016a) applied to plaque-level rather than tissue-level quantification, and would test whether the architectural co-localization is uniform across plaques or concentrated in a subset that defines the framework's prediction more precisely.

VIII.8 The ARIA-Fungal Burden Autopsy Prediction

The framework predicts that autopsy tissue from patients who died from severe ARIA on anti-amyloid antibody therapy will show, on adequate fungal staining, increased detection of fungal material in cerebral vasculature relative to comparable AD patients not on antibody therapy. The hemorrhagic and edematous foci should localize with vessel wall fungal deposits. The prediction follows from the framework's reading of ARIA as encapsulation-stripping signature in vascular fungal compartments (treated in §V.4). The autopsy infrastructure exists; severe ARIA cases on lecanemab and donanemab have been collected post-FDA approval; the antibodies necessary for fungal staining are commercially available. The analysis has not been performed and should be performed urgently given the active ongoing administration of these therapies to patients.

VIII.9 Pituitary Pathology in AD

The framework predicts that systematic examination of pituitary glands from AD patients at autopsy will reveal pathology distinct from age-matched cognitively normal controls, with the distinctive features including fungal elements adjacent to the gland, amyloid β deposition, and altered microadenoma frequency.

The iatrogenic AD literature establishes that human pituitaries can contain AD-relevant pathology in transmissible form. Jaunmuktane et al. (2015) reported moderate to severe Aβ parenchymal deposition and cerebral amyloid angiopathy in four of eight iatrogenic Creutzfeldt-Jakob disease patients aged 36 to 51, all of whom had received cadaver-derived pituitary growth hormone (c-hGH) in childhood. The Aβ deposition did not co-localize with prion deposition and was typical of AD-pattern pathology. Purro et al. (2018) confirmed the causal chain biochemically by demonstrating that archived c-hGH vials contained substantial Aβ peptide content with seeding capacity in mouse models. Banerjee et al. (2024) reported the first

premortem clinical descriptions of iatrogenic AD: eight c-hGH recipients developed dementia and AD biomarker changes three to four decades after pituitary growth hormone treatment, establishing iatrogenic AD as a clinical entity. These three studies together establish that pituitary tissue can serve as a source of transmissible AD pathology in humans.

The donor pituitaries from which contaminated c-hGH was extracted must therefore have contained Aβ. The iatrogenic literature does not address whether the donor pituitaries were pathologically unique or whether typical adult pituitaries (in subjects with subclinical or established AD) contain Aβ pathology that has gone unmeasured. The framework predicts the latter. In the framework's reading, chronic *Candida* governance load progresses across decades to eventually engage the pituitary as a governance control point, with hyphae establishing adjacent to the gland and interacting biochemically with exposed cell populations. The pituitary's proliferative response to local fungal signaling has been proposed within the framework's broader corpus (Craddock Pituitary and Thyroid, Case Study) as the mechanism producing microadenomas with heterogeneous immunohistochemical profiles (different pituitary cell populations responding to fungal contact at different positions). AD patients should therefore show pituitary pathology distinct from age-matched controls, including: amyloid β deposition detectable by standard immunostaining; fungal elements adjacent to or within the gland, detectable by Gomori methenamine silver staining, periodic acid-Schiff staining, anti-chitin antibodies per Pisa et al. (2016a) methodology, and multi-antibody anti-fungal panels per Pisa et al. (2015); elevated microadenoma frequency relative to age-matched controls; and pathology severity correlating with Braak stage and antemortem cognitive scores.

To the framework's knowledge, systematic examination of pituitary glands from typical AD patients at autopsy has not been performed. The non-iatrogenic AD pituitary literature consists primarily of clinical correlations (HPA axis dysregulation, hormone-level abnormalities) and incidental findings, rather than direct histopathological examination of pituitary tissue for AD-relevant pathology. The proposed analysis is tractable using existing autopsy infrastructure: brain banks that collect AD autopsy material typically also retain pituitary tissue, and the staining methodology is established in standard pathology practice. The analysis would discriminate the framework's prediction (AD pituitaries showing distinct pathology including fungal elements and Aβ deposition) from the null hypothesis (AD pituitaries indistinguishable from age-matched controls).

[*The pituitary appears across the framework's broader corpus as the governance control point eventually engaged by chronic Candida colonization. AD pituitary examination is one window into testing that broader thesis. The iatrogenic transmission literature provided unexpected proof that AD-relevant pathology exists in human pituitaries; the framework's contribution is the architecture that connects this finding to the rest of the AD trajectory. The pituitaries are sitting in brain bank freezers next to the cortical samples that have been examined hundreds of times. Someone could pull the matched specimens tomorrow.*]

VIII.10 Summary

The nine predictions assembled here range from the central therapeutic test (which requires a substantial Phase III trial) to retrospective analyses tractable in existing data. Several predictions are partially or fully corroborated in the existing literature: the dose-response between cumulative antibiotic exposure and AD risk (Kim et al. 2022), the cross-tissue comorbidity pattern of vitiligo and short stature with dementia (Chang et al. 2021; Jørgensen et al. 2020), fungal cell wall material detected in AD brain tissue (Pisa et al. 2016a; 2016b), the apoptotic mechanisms in AD-affected regions (Goel et al. 2022), and the iatrogenic transmission of AD pathology from contaminated pituitary growth hormone (Jaunmuktane et al. 2015; Purro et al. 2018; Banerjee et al. 2024). The framework's distinctive predictions beyond these corroborated findings consist of the deeper integration analyses: fungal-burden-stratified antibiotic dose-response; within-AD stratification by anti-SOX9 IgG for vitiligo and ISS comorbidity; per-plaque architectural quantification scoring cored senile plaques for fungal cores; the SOX9 transcript by MEGF10 protein by anti-SOX9 IgG triad measurement in AD patients; H3K9 lactylation in AD hippocampal astrocytes; dual fungal and apoptotic staining on the same sections in adequately powered cohorts; ARIA autopsy fungal-burden correlation; APECED cognitive aging in survivors past 50; the capsaicin-population AD trajectory analysis; and systematic histopathological examination of AD pituitary tissue. The central trial (multi-arm adaptive antifungal therapy) requires substantial investment but is comparable in scale to anti-amyloid antibody Phase III trials that have already been funded with negative results. The predictions are not contingent on each other; positive results in any one of the framework-specific integration analyses would constrain the framework substantially, and positive results in several would represent strong corroboration. The framework's epistemic posture is that the predictions are stakes in the published record. The empirical question is whether the field will perform the integration analyses the framework specifies.

§IX. Biomarker Stratification

The framework's mechanistic claims in §VI and §VII generate a clinical stratification approach that supports both the trial design in §VIII and routine clinical assessment of patients with cognitive complaints. The stratification rests on three measurable variables that, taken together, distinguish patients along the axes the framework identifies as causally relevant: fungal burden, host clearance machinery integrity, and host autoantibody response. Each variable is technically tractable with existing assays. The framework's claim is that the stratification is not currently performed in AD clinical practice because the framework that motivates it has not been adopted, and that performing the stratification would substantially improve both clinical decision-making and trial enrollment.

IX.1 The Core Triad: SOX9 Transcript, MEGF10 Protein, Anti-SOX9 IgG

The framework's central biomarker prediction is that AD patients can be characterized by the relationship between three measurements: SOX9 mRNA expression in astrocytes (transcriptional output), MEGF10 protein on astrocyte surfaces (functional clearance machinery), and circulating anti-SOX9 IgG titer (autoantibody response). The pattern of these three values, rather than any one in isolation, identifies the failed-compensation state described in §VI.

The expected normal pattern is moderate SOX9 transcript, adequate MEGF10 protein expression with the ratio of protein to transcript reflecting normal translation and post-translational processing, and absent or minimal anti-SOX9 IgG. Patients in this category have functional astrocytic clearance machinery; their AD pathology, if present, is driven by other mechanisms or by upstream factors the clearance system cannot adequately address (high fungal load, advanced disease).

The expected failed-compensation pattern is elevated SOX9 transcript, depressed MEGF10 protein with the protein-to-transcript ratio substantially reduced, and detectable anti-SOX9 IgG. Patients in this category have transcriptional output upregulated in compensation for autoantibody-mediated functional reduction, with the compensation failing because the autoantibody continues to neutralize the protein. The framework predicts these patients will respond differently to therapeutic interventions: SOX9-pathway boosting (which works in mouse models without autoantibodies) will produce limited benefit because the additional transcript is also neutralized, while antifungal therapy (which addresses the upstream stimulus that drives the autoantibody response over decades) may produce benefit by reducing the chronic *Candida* dysregulation that maintains the autoantibody-producing B cell clonal populations.

A third pattern is moderate SOX9 transcript, depressed MEGF10 protein, and absent anti-SOX9 IgG. Patients in this category have functional impairment from non-autoantibody causes, possibly post-translational regulatory abnormalities, microRNA-mediated suppression, or cellular dysfunction unrelated to the SOX9 pathway specifically. The differential prediction for this group is unclear and would emerge from the trial data itself.

[*The triad measurement is performed as follows. SOX9 transcript can be measured in plasma cell-free RNA using the methodology established for AD biomarker detection (Wu et al. 2025), or, more directly, in astrocyte-enriched preparations from postmortem brain (research only); plasma astrocyte-derived exosome panels can include SOX9-axis transcripts as a complementary modality. MEGF10 protein can be measured in astrocyte-derived exosomes isolated from peripheral blood, using established exosome isolation protocols followed by ELISA quantification. Anti-SOX9 IgG titer is measured by ELISA against recombinant SOX9 protein using standard autoantibody serology methodology (the same approach Hedstrand et al. 2001 used). All three measurements can be performed in living patients with peripheral blood draw and lumbar puncture. Remember: my job is to synthesize. I am uncovering what the science says to examine to further validate or invalidate portions of the framework.*]

IX.2 Fungal Burden Stratification

The complementary biomarker axis is direct fungal burden assessment. The available measurements:

Serum (1,3)-β-glucan (Fungitell or comparable assay). This is the test Alonso et al. 2014 used to demonstrate 28 of 29 AD patients positive. (1,3)-β-glucan is a fungal cell wall polysaccharide present in *Candida*, *Aspergillus*, *Pneumocystis*, and most yeasts and molds (notable exceptions: *Cryptococcus*, *Mucor*). The assay is quantitative; numerical values track with fungal burden. Existing clinical use is for diagnosis of invasive fungal infection in immunocompromised patients; the assay is FDA-approved and widely available in hospital laboratories.

Anti-fungal antibody panels. Quantitative ELISA assays for IgG against *Candida albicans*, *C. tropicalis*, *Malassezia*, *Aspergillus*, and other genera. Elevated titers indicate sustained host immune exposure to the relevant organism. Available in commercial laboratories for some genera (more developed for *Aspergillus* and *Candida* in invasive infection contexts), with research applications in chronic disease characterization expanding.

CSF mycology. Direct culture, PCR with ITS sequencing, or slot-blot for fungal antigens in cerebrospinal fluid. The Alonso 2015 paper demonstrated 10 of 10 AD positivity using slot-blot methodology. ITS sequencing is the more discriminating technique for genus and species identification but requires CSF cell pellets or larger volumes than routine clinical lumbar puncture provides. The technique is available in research and reference laboratories.

Gut mycobiome assessment. Stool sample collection followed by ITS sequencing characterizes the fungal community in the gut at the time of sampling. The Ling 2021 finding of *C. tropicalis* and *Schizophyllum commune* enrichment in AD patients with *C. albicans* underrepresentation in the lumen is the reference pattern. The framework's reading of the *C. albicans*-not-in-feces finding (the organism has transitioned to tissue-resident form, leaving feces depleted) is itself a stratification axis: patients showing this signature are predicted to be in advanced symbiont dysregulation with substantial tissue colonization, while patients showing intact luminal *C. albicans* with absent secondary occupants may be in earlier or less advanced dysregulation.

Plasma fungal-derived metabolites. Emerging assays for fungal-specific metabolites in peripheral blood (mannitol, arabinitol, specific lipids) provide additional burden assessment. These are less developed clinically but are likely to enter routine practice over the next decade.

IX.3 Composite Stratification: The Two-Axis Framework

The triad and the fungal burden measurements together produce a two-axis framework for AD patient classification:

Axis 1: Fungal burden (low to high). Combined assessment of serum (1,3)-β-glucan, antibody panels, and CSF mycology. The framework's prediction is that high-burden patients are most likely to respond to antifungal intervention, with effect size scaling with baseline burden.

Axis 2: Host clearance integrity (intact to compromised). Combined assessment of the SOX9-MEGF10 transcript-protein ratio and anti-SOX9 IgG. The framework's prediction is that patients with intact clearance machinery (intact ratio, low autoantibody) are most likely to benefit from interventions that boost clearance, while patients with compromised clearance machinery (decoupled ratio, elevated autoantibody) are most likely to require interventions that reduce the upstream organism load directly.

The two-axis framework produces four quadrants:

Q1: High burden, intact clearance. Patients with substantial fungal load whose host machinery can clear it if upstream load is reduced. Predicted strongest response to antifungal therapy, with both fungal load reduction and concurrent benefit from intact clearance machinery.

Q2: High burden, compromised clearance. Patients with substantial fungal load and autoantibody-decoupled clearance. Predicted partial response to antifungal therapy alone; may require combined antifungal plus immunomodulatory approach to address the autoantibody component. The most architecturally complex AD presentation.

Q3: Low burden, intact clearance. Patients with limited fungal load and intact clearance. Predicted minimal benefit from antifungal therapy. Their AD pathology, if present, is likely driven by other mechanisms; alternative interventions warranted.

Q4: Low burden, compromised clearance. Patients with limited fungal load but autoantibody-decoupled clearance. Unusual quadrant. May represent post-fungal-clearance autoantibody persistence or a different upstream driver entirely. Predicted to respond to immunomodulatory therapy targeting the autoantibody response without significant antifungal component.

Future trial designs may stratify enrollment by these quadrants. The framework's prediction is that response to antifungal therapy will track with quadrant assignment as described above.

IX.4 The APOE4 Stratification

APOE4 status interacts with the framework's predictions in multiple ways and warrants specific stratification consideration. The lecanemab Clarity AD trial showed that anti-amyloid antibody therapy did not produce benefit in APOE4 carriers (van Dyck et al. 2023; Imbimbo et al. 2024). The framework's reading is that APOE4 carriage represents a distinct host-symbiont architecture (altered lipid handshake, different ApoB metabolism, different cerebrovascular biology) in which removing encapsulation produces particularly poor outcomes because the encapsulation has been deployed against a more challenging fungal burden in a more vulnerable vasculature. The ARIA risk in APOE4 homozygotes (approaching 40 percent in some lecanemab

subgroups; van Dyck et al. 2023) is consistent with this reading: stripping encapsulation off vascular fungal material in APOE4 carriers exposes more fungal material in more fragile vessels.

The framework's prediction for APOE4 carriers in an antifungal trial is more positive than for the same carriers in an anti-amyloid antibody trial. APOE4 carriers should show benefit from antifungal therapy if the framework is correct, because the intervention addresses the underlying organism burden rather than the host's defensive structure. The differential response (no benefit to APOE4 carriers from anti-amyloid antibodies; benefit predicted to APOE4 carriers from antifungal therapy) is a falsifiable framework claim.

[*The APOE4 stratification implication is testable through the trial design proposed in §VIII. If APOE4 carriers show benefit from antifungal therapy in the trial, the framework's reading of the lecanemab APOE4 failure as host-architecture-specific encapsulation-stripping risk is corroborated, and the clinical-practice implications follow. The framework's claim is not that APOE4 stratification should precede the trial, but that the trial should record APOE4 status carefully so the stratified response pattern can be observed.*]

IX.5 Sex Stratification

The lecanemab trial also demonstrated absent benefit in women, with effect concentrated in male non-APOE4 carriers. Two-thirds of AD patients are women. The framework's reading of the sex difference connects to reservoir dynamics: women have additional *Candida* reservoirs (vaginal mucosa) cycling across decades of reproductive years, with hormonal modulation of mucosal immunity producing sex-specific colonization patterns and presumably sex-specific disease architecture.

The framework's prediction for women in an antifungal trial is that response should be present and potentially larger than in men, given women's higher baseline organism burden and different reservoir dynamics. The prediction is again falsifiable: if women show no benefit from antifungal therapy in a properly stratified trial, the framework's reading of sex-specific reservoir dynamics needs revision.

IX.6 Cross-Tissue Comorbidity Stratification

Patients with documented vitiligo, idiopathic short stature in family history, recurrent vaginal candidiasis history, recurrent oral thrush history, or other cross-tissue manifestations of the chronic *Candida* dysregulation architecture (§VI.7) should be flagged in clinical assessment as possessing the cross-tissue signature. The framework's prediction is that AD patients with these comorbidities have stronger autoantibody profiles and stronger fungal burden than AD patients without them, and that the trial response stratification by these clinical features should track with the laboratory stratification described above. Clinical assessment of these comorbidities is essentially free; recording them at trial enrollment and in routine AD clinical evaluation requires only attention to the clinical history.

IX.7 Implementation Sequencing

The biomarker stratification approach described above is not a precondition for the antifungal trial proposed in §VIII. The trial is the priority. The stratification approach is what should follow if the trial validates the framework's central therapeutic prediction. The sequencing matters: if the framework's claim that antifungal therapy produces meaningful cognitive benefit in early AD is correct, the trial will demonstrate it without requiring the full stratification machinery to be in place beforehand. If the trial does not demonstrate it, the stratification machinery is unlikely to rescue the framework, and resources spent assembling it would have been better spent elsewhere.

The pragmatic sequencing is therefore as follows. The antifungal trial proceeds with the simplest enrollment criteria consistent with reasonable trial design: biomarker-confirmed early AD or amnestic MCI, evidence of fungal burden by serum (1,3)-β-glucan as the principal entry criterion, standard exclusions for safety. The trial's adaptive multi-arm structure permits efficacy signals to inform clinical practice on the timeline described in §VIII.1. If positive efficacy is demonstrated in any arm, the stratification approach in §IX.1 through §IX.6 becomes the natural next research priority, with the goal of identifying which patients respond most strongly and which therapeutic protocols match which patient profiles. The stratification refines the treatment; the trial establishes whether the treatment works at all.

The sequencing also constrains what can be claimed about the framework on the basis of the trial alone. A positive trial result demonstrates that antifungal therapy produces clinical benefit in early AD; it does not, by itself, establish the SOX9-MEGF10-Hk1 mechanism in §VI or the autoantibody-decoupling prediction. Those claims are partially independent of the trial result; they would survive a positive trial without being fully tested by it, and they would survive a null trial as predictions about which patient subpopulations the trial may have enrolled in unrepresentative ways. The trial is the priority because it tests the framework's most actionable claim, not because it tests every framework claim.

> [*The sequencing reflects the framework's epistemic commitments. The most actionable prediction is also the most testable, the most clinically consequential, and the most resource-justified. The mechanistic and stratification predictions are tractable downstream investigations that follow naturally from a positive trial result. Keeping them downstream rather than upstream prevents the framework from accumulating preconditions that delay the central question. The central question is whether antifungal therapy produces cognitive benefit in AD. Everything else can wait.*]

The next section addresses the institutional pattern that has prevented integration of the existing evidence base, and considers what conditions are required for the integration to proceed.

§X. Institutional Analysis

The published evidence assembled in §II through §VII has accumulated across more than a decade in major peer-reviewed venues. The integration the framework performs in this paper has not been performed by the field. The drug-screen results converging on antifungal compounds have not produced antifungal trials in AD. The cerebrospinal fluid diagnostic pathway has not entered clinical practice. The patient population is being treated with anti-amyloid antibodies that produce biomarker improvement without functional benefit, with adverse events that the framework reads as encapsulation-stripping signature, in subpopulations (women, APOE4 carriers) for whom the antibodies show no demonstrated benefit at all. The framework's claim about this pattern is not that it reflects bad faith on the part of individual researchers, clinicians, or institutions. The framework's claim is that it reflects how scientific fields respond to evidence that does not fit their dominant integrative framework, and that the response pattern has historical precedent.

X.1 The Documented Timeline

The brain-colonization evidence and its therapeutic implications have arrived in a sequence the field could have integrated at multiple points:

2010. Soscia et al. demonstrate amyloid β as antimicrobial peptide with potent activity against *Candida albicans*. The reframe of amyloid as antimicrobial defense is published in *PLOS ONE*.

2014. Alonso et al. demonstrate fungal proteins, DNA, and species identification in AD brain tissue. Companion paper demonstrates 28 of 29 AD patients positive for systemic disseminated fungal polysaccharides on Fungitell assay. The foundational pair establishing fungal-AD presence is published in *Journal of Alzheimer's Disease* and *European Journal of Clinical Microbiology and Infectious Diseases*. The papers explicitly call for antifungal clinical trials in AD.

2015. Pisa et al. demonstrate fungal cells and hyphae across multiple brain regions in 100 percent of AD patients sampled, with 0 percent in controls, including intracellular and intranuclear localization in neurons. Companion CSF paper demonstrates fungal antigens in 10 of 10 AD CSF samples. *Scientific Reports* and *Journal of Alzheimer's Disease*.

2016. Kumar et al. demonstrate Aβ as antimicrobial protection in mouse and worm models of AD; the host's amyloid response is shown to be functional defense rather than dysregulation. *Science Translational Medicine*. Pisa et al. (2016a) detect fungal cell wall material directly in AD brain tissue using anti-chitin antibodies plus antibodies against fungal enolase and β-tubulin. *Frontiers in Microbiology*. Pisa et al. (2016b) demonstrate that corpora amylacea in AD brain tissue stain positive with specific antifungal antibodies. *Frontiers in Neuroscience*. Cestari et al. report elevated systemic cytokines (IL-1β, TNF-α, IL-6) correlated with oral infection prevalence in AD and MCI patients relative to controls. *Journal of Alzheimer's Disease*.

2017. Carrasco group writes the fungal-AD chapter for the *Handbook of Infection and Alzheimer's Disease*, a multi-author reference work. The chapter explicitly proposes fungal infection as etiological contributor.

2018. Eimer et al. extend the antimicrobial encapsulation finding to viral infection; HSV-1 seeds Aβ deposition that physically entraps virions in protective architecture. *Neuron*. Aragón et al. document poorer oral health in AD patients in a multicenter case-control study. *Clinical Oral Investigations*.

2019. Wu et al. demonstrate causal mechanism in mouse: *C. albicans* crosses blood-brain barrier, forms FIGGs morphologically identical to cored AD plaques, with amyloid β deposition around fungal cores and associated cognitive impairment. *Nature Communications*.

2020. Nagpal et al. demonstrate that a modified Mediterranean ketogenic diet administered to subjects with mild cognitive impairment shifts both gut mycobiome composition and cerebrospinal fluid AD markers (amyloid β, tau) within months. *EBioMedicine*. Jørgensen et al. analyze 666,333 Danish men in a nationwide cohort and demonstrate an inverse hazard ratio of 0.90 per z-score increase in adult height for subsequent dementia diagnosis, with the association persisting in within-brother and within-twin-pair analyses controlling for shared familial factors. *eLife*.

2021. Kumari et al. report blind FDA archive screen against Aβ aggregation; top hit is caspofungin, an echinocandin antifungal. *Molecular and Cellular Neuroscience*. Vigasova et al. consolidate the multi-pathogen AD literature in *Microbial Cell Factories*. Ling et al. report gut mycobiome alterations in 88 Chinese AD patients with *C. tropicalis* enrichment and reduced *C. albicans* in feces. *Frontiers in Cell and Developmental Biology*. Chang et al. analyze Taiwan National Health Insurance records and demonstrate a 12.22-fold adjusted hazard ratio for AD in vitiligo patients relative to matched controls (n=1,320 vitiligo, 5,280 controls). *Journal of Dermatology*.

2022. Kim et al. analyze 313,161 South Korean adults and demonstrate a dose-response association between cumulative antibiotic exposure and dementia incidence: ≥91 cumulative prescription days produces a 1.46-fold adjusted hazard ratio for AD specifically, with use of five or more antibiotic classes producing an additional 1.34-fold hazard ratio. *Frontiers in Pharmacology*. Goel et al. publish a comprehensive review of regulated cell death mechanisms in AD covering apoptosis, necroptosis, pyroptosis, ferroptosis, and autophagy-dependent cell death, with documentation of mitochondrial pathway activation and caspase cascade involvement in AD-affected brain regions. *Frontiers in Molecular Neuroscience*.

2023. Wu et al. characterize molecular mechanism: fungal Saps cleave host APP into Aβ-like peptides that activate antifungal immunity. *Cell Reports*. Lecanemab Clarity AD trial publishes with 0.45-point CDR-SB difference at 18 months and absent benefit in women and APOE4 carriers (van Dyck et al. 2023).

2024. Xie et al. report independent fragment-based drug discovery screen returning seven antifungals across five mechanistic classes. *ACS Chemical Neuroscience*. Golipoor et al. compare oral fungal composition directly in AD versus non-AD patients admitted to a neurology clinic and report 1.6-fold higher oral fungal prevalence in AD, with *C. albicans* dominant in both groups (80 percent of AD samples versus 40 percent of non-AD samples) and reduced fungal diversity in AD samples. *Frontiers in Cellular and Infection Microbiology*.

2025. Choi et al. characterize SOX9-MEGF10 phagocytic clearance pathway in astrocytes. *Nature Neuroscience*. Chen et al. characterize SOX9-Hk1-lactate-H3K9 lactylation inflammatory pathway in astrocytes. *Nature Communications*. Cornitius (UTSA dissertation) demonstrates gut-to-brain mechanistic chain in mouse and human iPSC organoid models.

2026. Comprehensive evidence review of 17 anti-amyloid antibody trials encompassing more than 20,000 participants concludes that absolute effects on cognitive decline are "absent or trivial."

The pattern is clear. Foundational evidence of fungal involvement landed in 2014. Direct detection of fungal cell wall material in AD brain was published in 2016. Causal mechanism in animal models was published in 2019. Population-scale corroboration of cross-tissue comorbidity (vitiligo, short stature) and cumulative antibiotic exposure as AD/dementia risk factors accumulated from 2020 to 2022. Convergent drug-screen evidence accumulated from 2021 to 2024. Direct comparison of oral fungal composition in AD versus non-AD patients was published in 2024. Cellular mechanism for the host clearance failure was characterized in 2025. Across this twelve-year window, no major Phase III trial of antifungal therapy in AD has been registered. The evidence has been published in *Nature Communications*, *Nature Neuroscience*, *Science Translational Medicine*, *Cell Reports*, *Neuron*, *Scientific Reports*, *PLOS ONE*, *eLife*, *EBioMedicine*, *Journal of Alzheimer's Disease*, *Journal of Dermatology*, *Clinical Oral Investigations*, *ACS Chemical Neuroscience*, *Molecular and Cellular Neuroscience*, *Microbial Cell Factories*, and multiple Frontiers journals (Microbiology, Neuroscience, Pharmacology, Molecular Neuroscience, Cellular and Infection Microbiology, Cell and Developmental Biology, Aging Neuroscience). The evidence is not obscure. It is not contested in any specific way; the data has not been refuted, only not integrated.

X.2 The Helicobacter Pylori Parallel

The historical precedent is well documented. Marshall and Warren proposed *Helicobacter pylori* as the causative agent of peptic ulcer disease in 1982. The proposal contradicted the established framework of acid hypersecretion as the proximate cause and acid-suppression therapy as the appropriate treatment. The pharmaceutical industry had built a multi-billion-dollar revenue stream around acid-suppression therapy (H2 blockers, then proton pump inhibitors) by 1982. The proposal was met with skepticism, professional resistance, and active dismissal for over a decade. The first NIH consensus conference acknowledging *H. pylori* as ulcer causation was held in 1994, twelve years after the initial proposal. Field-level acceptance

and integration into standard treatment protocols took until approximately 2005, twenty-three years after the original proposal. Marshall and Warren received the Nobel Prize in Physiology or Medicine in 2005.

The parallel is not exact. The Marshall-Warren proposal addressed a single causative agent in a relatively simple disease with definitive endpoint markers (ulcer presence, ulcer healing). The fungal-AD framework addresses a complex, chronic, multi-decade dysregulation with cognitive endpoints that are inherently noisier than ulcer healing. The pharmaceutical industry investment in anti-amyloid therapy substantially exceeds the investment in acid-suppression therapy in the 1980s, both in absolute terms and as a fraction of the relevant therapeutic area. The institutional inertia operating against fungal-AD integration is consequently larger than the inertia operating against *H. pylori* integration in 1982.

The parallel is suggestive in two specific ways. First, the time-scale of resistance to integration was approximately 12 to 23 years for *H. pylori*. The fungal-AD evidence has been accumulating for 12 years as of this paper. By the *H. pylori* timeline, the integration may be on the verge of occurring naturally or it may be 10 to 15 years away from occurring. Second, the resistance was overcome through accumulated empirical demonstration rather than through conceptual persuasion. Marshall famously self-administered *H. pylori* and developed gastritis to demonstrate the causal mechanism; ulcer-eradication data accumulated through the 1990s; randomized controlled trials of antibiotic therapy for ulcers eventually became overwhelming. The framework's reading is that the fungal-AD integration will proceed similarly: through trial data demonstrating efficacy of antifungal intervention, with the conceptual integration following the empirical demonstration rather than preceding it.

> [*The H. pylori parallel suggests both how long the integration takes and how it eventually occurs. The framework's contribution to acceleration is to specify the trial that needs to be performed and to articulate the architectural reasoning that motivates it. The trial itself is the inflection point. The integration follows the trial; the trial does not follow the integration.*]

X.3 The Patient Population and Patient-Generated Documentation

The institutional gap is not only academic. The r/Candida community on Reddit (the largest of multiple patient-driven platforms) has accumulated approximately 28,000 members and draws on the order of 25,000 weekly visitors. The visitor-to-member ratio indicates that substantially more people are consulting the documentation than have enrolled in the community, presumably searching for answers the medical system has not provided. The participants document chronic presentations that the clinical literature has neither integrated nor effectively addressed: skin involvement, gastrointestinal symptoms, persistent brain fog, fatigue, autonomic dysfunction, and in some cases severe medical decompensation, with many reporting near-zero substantive support from primary care or specialty medicine. A nontrivial fraction document at a level approaching scientific rigor, tracking dietary interventions, antifungal

courses, symptom timelines, and laboratory work across years. The patient population has been generating the longitudinal observational record that clinical research has not. The framework's reading is that this body of self-documented experience is real signal about a disease the field has declined to study, not misattribution of unrelated symptoms to a fashionable cause.

X.4 Why the Integration Has Not Occurred

The framework offers no dispositive explanation for why the integration has not occurred. Several contributing factors are visible in the published record and in the institutional structures of academic medicine and pharmaceutical development. The framework names them descriptively, without claiming any one is decisive.

The dominant integrative framework in AD research has been the amyloid hypothesis, with three decades of investment in target engagement, biomarker development, drug development, and clinical trial infrastructure. Findings that do not fit the dominant framework face higher integration costs than findings that do; the cost is both intellectual (requiring reframe of established interpretations) and institutional (requiring redirection of established funding streams, training programs, and clinical practice patterns). The fungal-AD evidence requires substantial reframe; the integration cost is correspondingly high.

Pharmaceutical investment has concentrated in target classes consistent with the dominant framework. Anti-amyloid antibodies, secretase inhibitors, anti-tau approaches, and anti-inflammatory approaches have received the dominant share of clinical trial investment. Antifungal approaches have not been pursued because no major pharmaceutical sponsor has identified fungal infection as the AD therapeutic target. Investigator-initiated trials of approved antifungals would be possible in principle, but they require funding sources outside the major pharmaceutical pipelines and require institutional support that is not currently in place.

Clinical infrastructure for fungal-AD diagnostic assessment has not been built. CSF mycology is performed in fungal infection clinical contexts but not as part of routine AD clinical assessment. Fungitell testing is available but not ordered for AD workup. Anti-fungal antibody panels are available but not in standard AD clinical pathways. The diagnostic infrastructure exists in mycology and infectious disease departments but not in neurology and dementia clinics. The cross-departmental integration that the framework's reading would require has not occurred at scale.

Individual researchers who have advanced fungal-AD findings have been treated as adjacent rather than central to AD research. The Carrasco group in Madrid has produced sustained work since 2014; the Wu/Corry group at Baylor has produced sustained work since 2019; the Itzhaki HSV-1 work has continued for decades. These contributions appear in major journals and accumulate citations, but they have not produced integration into dominant AD frameworks. The pattern is consistent with the *H. pylori* historical precedent: foundational work treated as parallel rather than central until empirical demonstration becomes overwhelming.

[*The framework names these contributing factors without asserting that any one is decisive. The pattern is multi-factorial and follows the historical pattern of similar reframes in medical history. The framework's claim is not that the integration has been actively suppressed; the framework's claim is that the integration has not occurred for reasons consistent with how scientific fields generally respond to evidence that does not fit their dominant framework, and that the integration will eventually occur through the same pathway it has occurred for analogous reframes: through trial data that becomes overwhelming.*]

X.5 What Would Accelerate Integration

The trial proposed in §VIII.1 is the most direct path to integration. A multi-arm adaptive trial demonstrating efficacy of antifungal therapy in early AD, with effect size comparable to or exceeding the framework's prediction (CDR-SB difference of 1.0 or greater), would shift the dominant framework substantially. Adaptive design features permitting early efficacy signals to inform clinical practice on a timeline of 12 to 18 months rather than 4 to 7 years would accelerate the integration further.

Funding for the trial does not currently exist. The pharmaceutical industry has no commercial incentive to repurpose generic antifungal drugs for AD; the off-patent status of fluconazole and the limited remaining patent life on echinocandins reduce the commercial return on investment to levels well below typical Phase 3 trial costs. The trial is therefore unlikely to be funded through pharmaceutical industry investment in the absence of a proprietary new agent. Government funding (NIH, EMA) and philanthropic funding (Alzheimer's Association, Bill and Melinda Gates Foundation, BrightFocus) are the most plausible sources. The trial cost is substantial but is comparable to or smaller than the cost of failed Phase 3 anti-amyloid antibody trials that have already been funded.

The framework's claim is that the trial deserves the funding because the prediction is mechanistically grounded, the diagnostic infrastructure exists, the drug candidates exist and are FDA-approved across three mechanism classes, and the disease in question affects tens of millions of people with no current effective treatment. The cost of not running the trial is substantially greater than the cost of running it.

Additional accelerants include retrospective analyses in existing patient cohorts (lifetime antibiotic exposure × AD risk; capsaicin population × AD epidemiology; APECED cohort × accelerated cognitive aging), which require no new patient recruitment and could be performed on existing data within months. The ARIA-fungal-burden autopsy correlation analysis (§VIII.8) is similarly tractable in existing brain bank infrastructure. None of these analyses require trial-scale funding; they require attention, framing, and the willingness to ask the questions the framework motivates.

X.6 Summary

The institutional pattern that has prevented integration of the fungal-AD evidence is multi-factorial, historically precedented, and consistent with how scientific fields generally respond to reframes of dominant interpretive structures. The framework names the pattern without asserting bad faith. The trial proposed in §VIII.1 is the most direct path to acceleration. The pattern will eventually be overcome through accumulated empirical demonstration, as the analogous *H. pylori* pattern was overcome over 23 years from initial proposal to field-level integration. The framework's contribution to acceleration is to specify the trial that needs to be performed and to articulate the architectural reasoning that motivates it.

The patient population, in the meantime, continues to deteriorate. The pharmaceutical investment in anti-amyloid antibody therapy continues. The diagnostic infrastructure for fungal-AD characterization exists but is not deployed. The drug candidates exist but are not tested in this indication. The framework's claim is that this state of affairs is changeable, and that the change begins with the trial.

§XI. Conclusion

This paper has performed an integration that the field has not. The integration follows from taking three categories of published evidence seriously simultaneously: the documented presence of *Candida albicans* and other fungi in Alzheimer's disease brain tissue, the demonstrated antimicrobial peptide function of amyloid β, and the convergent return of antifungal compounds as top-ranked hits in blind drug screens against amyloid β aggregation. Each category is established in the literature. Each category has been treated as adjacent rather than central to mainstream AD research. Read together, they describe a single coherent disease architecture that the framework names.

The architecture is as follows. *Candida albicans* establishes commensal residence in the gastrointestinal tract of approximately half the human population. Across decades of dietary substrate availability, antibiotic exposure, and accumulated immune drift, the host-symbiont relationship transitions in a substantial subset of hosts from luminal commensalism to tissue-invasive dysregulation. Hyphal morphology and candidalysin secretion enable epithelial barrier disruption; fungal aspartyl proteinases enable blood-brain barrier disruption and direct cleavage of host APP into amyloid β peptides. The organism establishes brain colonization across multiple regions, with vascular involvement, parenchymal granuloma formation, and intracellular and intranuclear residence in host neurons. The host deploys amyloid β as antimicrobial defense, encapsulating the organism in the structures conventionally identified as senile plaques. The astrocytic SOX9-MEGF10-Hk1 architecture is the host's clearance and maintenance system for the encapsulation. Chronic *Candida* exposure produces autoantibodies against SOX9 and SOX10 in a substantial fraction of hosts, selectively disabling the phagocytic clearance arm while leaving the inflammatory arm operational. The compensation fails. Amyloid burden accumulates not because the host is producing too much defensive encapsulation but because the host cannot clear the encapsulation it produces. The symptomatic disease emerges as the chronic locked-in

inflammatory state that the failed compensation produces. Late-stage AD is the terminal manifestation of this architecture.

Within this reading, the anti-amyloid antibody program is removing the host's defensive encapsulation around live brain pathogens. The biomarker improvement (PET-detectable amyloid clearance) reflects the encapsulation removal. The functional failure (no meaningful cognitive benefit) reflects the persistence of the encapsulated organism. The ARIA adverse event class reflects the encapsulation-stripping signature in vascular compartments where fungal cells lodge. The differential failure of anti-amyloid antibodies in women and APOE4 carriers reflects the population-specific host architectures the framework's reservoir-and-encapsulation reading would predict to respond differently. None of these patterns is paradoxical within the framework. All of them are paradoxical within the conventional framework, which lacks the architecture that integrates them.

The therapeutic implication is direct. Antifungal therapy targeting *Candida albicans* in early-stage AD with documented fungal burden should produce cognitive benefit substantially exceeding that of approved anti-amyloid antibodies. The prediction is testable through the multi-arm adaptive trial design proposed in §VIII.1. The diagnostic infrastructure exists. The drug candidates exist and are FDA-approved across three mechanism classes. The patient population is identified. The trial has not been performed.

The framework's claim about why the trial has not been performed is descriptive rather than accusatory. The pattern is consistent with how scientific fields respond to evidence that does not fit dominant integrative frameworks, follows the historical precedent of the *Helicobacter pylori* reframe in peptic ulcer disease, and operates through institutional inertia rather than active suppression. The integration will eventually occur through accumulated empirical demonstration, as the analogous reframes have occurred. The systemic consequences of the integration are developed in the Implications paper (Craddock, Implications); the historical institutional response patterns to convergent research in related areas are documented in a companion analysis (Craddock, Exposé). The framework's contribution to acceleration is to specify the trial that needs to be performed and to articulate the architectural reasoning that motivates it. The trial is the inflection point. The integration follows the trial.

The author notes that the present paper differs from the historical pattern in a structural respect: all cited evidence in this work exists in peer-reviewed publications, open-access repositories, and publicly verifiable scientific sources. The integration the framework provides here is openly available for the field's adoption or refutation, and the author is confident the present work will not be subject to the institutional response pattern documented in the historical analysis.

The framework positions Alzheimer's disease as the brain-stage manifestation of the same symbiont dysregulation the Redacted Science corpus documents in earlier-life stuck states: T2D, obesity, anorexia, IBS, Parkinson's, endometriosis (Craddock, Stuck State). The cross-disease pattern is not coincidental in the framework's reading. The same organism, the same

sensing architecture, the same governance machinery that produces metabolic dysregulation in midlife produces the brain-stage manifestation in late life when cumulative dysregulation reaches the cellular compartments most resistant to repair. AD is the terminal expression of the lifetime arc.

The framework's distinctive feature is that its central mechanistic claim generates testable predictions across multiple disease states, multiple compartments, and multiple time scales from a single architectural reading. Conventional AD frameworks generate predictions only within AD itself; the framework predicts AD trajectory, *Candida*-favoring exposure correlations across disease states, capsaicin-population epidemiology, APECED cognitive aging, cross-tissue comorbidity patterns, ARIA-fungal-burden autopsy correlations, and direct therapeutic outcomes. Some predictions are tractable in existing data without new patient recruitment. Some predictions require modest new investments in retrospective analysis. The central prediction (antifungal therapy efficacy in AD) requires a substantial trial, which deserves the substantial investment because the disease affects tens of millions of people with no current effective treatment.

The framework's claim is not that *Candida albicans* is the only contributor to Alzheimer's disease. The framework's claim is that *Candida albicans* is the central organism whose chronic dysregulation produces the architectural conditions the field has been describing in fragments, and that the mechanism integrates those fragments into a coherent etiology with testable predictions and direct therapeutic implications. The integration is the contribution. The trial is the test. The patients deserve both.

[*The framework's case is now on the published record. The mechanistic chain is documented across more than fifty peer-reviewed papers from independent research groups across three continents. The drug-screen evidence converges across two independent screening methodologies on the same therapeutic class. The diagnostic infrastructure exists in living patients. The drug candidates are FDA-approved across three mechanism classes. The trial design is specified. The funding sources are identifiable. The patient population is documented and deteriorating. The historical precedent for resolution is named. There are no remaining technical, conceptual, evidentiary, or pharmacological obstacles to performing the test the framework specifies. There are no excuses left.*]

§XII. References

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Note on verification. All references in the above list have been verified for first author, year, journal, and DOI as of the writing date. Readers are encouraged to confirm specific claims by consulting the cited primary sources directly. The framework's empirical claims do not rest on any single citation; the integration draws on the corpus as a whole.