

The Saline Oscillation Hypothesis: Endocannabinoid-Mediated Fungal-Hominid Co-Evolution in the East African Rift Valley

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Abstract

This paper extends the *Mammalia candidus* pan-mammalian co-evolution hypothesis (Craddock, 2026a) by proposing a specific environmental mechanism: cyclical lake salinity variation in the East African Rift Valley during the Plio-Pleistocene as the driver that activated and deepened the symbiosis between *Candida* species and hominid hosts. Drawing on paleoclimatological evidence of alternating humid and arid periods producing dramatic lake-level and salinity oscillations (Maslin et al., 2014; Trauth et al., 2005), paleoanthropological evidence of concurrent hominid speciation and encephalization events (Shultz and Maslin, 2013), and established literature on the endocannabinoid system (ECS) as a conserved master regulatory system across mammals (Elphick, 2012), we propose that periodic exposure to increased electrolyte concentrations in drinking water followed by freshwater periods producing electrolyte disruption analogous to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) provided the environmental conditions under which a fungal symbiont capable of managing host perfusion and electrolyte balance gained decisive selective advantage.

The symbiont's capacity to fill this role is not limited to the ECS. We present a synthesis of peer-reviewed evidence demonstrating that *Candida albicans* occupies a unique position in the mammalian internal ecology: it is the only organism in the host microbiome that simultaneously signals across kingdoms (to bacteria, competing fungi, and the mammalian host), possesses physical tissue mobility through hyphal morphological transition, and accesses the host's endogenous receptor infrastructure. Confirmed molecular targets of *C. albicans* metabolites include nuclear transcription factors (FXR, PPARs), voltage-gated calcium channels, GABA-A neurotransmitter receptors, the GLP-1 incretin system, cholinergic receptors, and multiple arms of both innate and adaptive immunity. The endocannabinoid system, while the primary and most ancient interface, represents the trunk of a signaling architecture whose canopy extends across the broader GPCR superfamily and beyond. We reinterpret farnesol, the first quorum-sensing molecule identified in a eukaryote (Hornby et al., 2001), not as a self-regulatory signal but as a multi-target effector molecule deployed to manage the host environment, consistent with the twenty-two-year absence of any identified farnesol receptor in *C. albicans* itself.

We further propose that the social component of the co-evolutionary architecture was initiated before the salinity oscillations through the discovery and communal use of exogenous phytocannabinoids, which promoted peaceful social bonding, group cohesion, and cooperative behavior. This pre-linguistic social flywheel, reinforced epigenetically through transgenerational cannabinoid-induced methylation changes, established cooperative social structure before the emergence of language. Language did not create the co-evolutionary trinity of symbiont, host physiology, and social structure. It completed it, and allowed it to accelerate.

Single-cell transcriptomic evidence (Dumeaux et al., 2023) demonstrating pre-positioned bet hedging, distributed survival strategies, and controlled genome destabilization in *C. albicans* populations is reinterpreted within this co-evolutionary framework as architectural rather than merely pathogen-adaptive, consistent with an organism refined across approximately 200 million years of mammalian co-evolution. It is the ultimate survivor: a biochemical computer continuously recalculating what moves might be required next. The *C. albicans* genome (14.3 Mb, approximately 6,400 genes) encodes over 1,300 genes with no orthologs in other yeast species, the majority of which remain functionally uncharacterized.

We designate the symbiont-active hominid phenotype *Homo candidus* and argue that a subsequent genetic shift in cardiac architecture from suction-dominant to pump-dominant circulation disrupted the co-evolutionary trinity, producing the modern human condition in which the symbiont persists commensally but can no longer execute its full physiological program. Fifteen testable predictions are presented, including proposed experiments in simulated gastric environments, comparative mycobiome analysis of Rift Valley populations, computational genomic analysis of uncharacterized *C. albicans* genes using biological foundation models, and molecular dating of the *C. albicans* / *C. dubliniensis* divergence.

Keywords: endocannabinoid system, *Candida albicans*, fungal-hominid co-evolution, East African Rift Valley, Plio-Pleistocene paleoclimate, saline oscillation, pituitary perfusion, language evolution, *Homo candidus*, SIADH, epigenetic methylation, GPCR, farnesol, candidalysin, Ece1, Kex2, peptide transporters, prohormone convertase, LILR, peptide mimicry, neuropeptides cross-kingdom signaling, bet hedging, GLP-1, cholinergic signaling, oxylipin, prostaglandin E₂, arachidonic acid, Th1/Th2 polarization, molecular mimicry, eicosanoid, pH manipulation, potassium homeostasis, Na⁺/K⁺-ATPase reversal, candidalysin pore formation, bioelectric signaling, Tok1, ammonia excretion, extracellular vesicles, small RNA, cross-kingdom RNA interference, DHX29, codon optimality, vesicle cargo, bidirectional signaling

Methodological Note on Sources and Extraordinary Circumstances

This paper cites several works by the author (Craddock, 2013; 2022; 2026a; 2026b). In standard academic practice, self-citation of this density would warrant scrutiny. The circumstances here are not standard.

The theoretical framework described in this paper derives in part from a 1995 peer-reviewed article that was subsequently redacted by removal from institutional access and citation indices under circumstances the author has documented extensively (Craddock, 2026b). The original article described a longitudinal cohort study of a physiological condition involving fungal-host interaction, endocannabinoid system modulation, and progressive organ system changes. The author encountered this article in 1995, retained key observations from it, and over the subsequent thirty years developed the condition described therein, becoming, in effect, both researcher and subject.

Because the original source was redacted, no conventional citation chain exists. The author's self-published works represent the only extant documentation of both the original findings and the thirty-year longitudinal case study that followed. These works are distributed across censorship-resistant platforms (IPFS, Nostr, GitHub) and indexed by major search engines. The author's identity as the primary source for "Redacted Science" is independently verifiable via Google and other search indices.

The self-citations in this paper are not circular. They reference: (1) observational data from a 30-year longitudinal case study that cannot be obtained from any other source, (2) a theoretical framework (the *Mammalia candidus* hypothesis) that extends established peer-reviewed literature into novel territory, and (3) historical documentation of a redacted research program. The peer-reviewed citations in this paper (Maslin et al., Shultz and Maslin, Elphick, Pacioni et al., Markey et al., Ren et al., and others) provide the independent evidentiary scaffolding. The self-citations provide the connective architecture that no other author is positioned to supply. Readers are encouraged to verify all claims independently.

Note on Novelty

The pulsed climate variability hypothesis (Maslin et al., 2014; Maslin and Trauth, 2009; Maslin, Shultz, and Trauth, 2015) established that East African Rift Valley lake oscillations are statistically correlated with hominid speciation, encephalization, and dispersal events. However, the authors explicitly noted that "the actual evolution mechanisms, which led to early hominins are still unclear and continue to be debated" (Maslin et al., 2014). Existing hypotheses linking salt to human evolution focus on dietary sodium intake through aquatic foods as a source of brain-building nutrients such as DHA (Cunnane, 2005), or on the evolutionary conservation of sodium appetite as a physiological drive (Leshem, 2009). Separately, a substantial literature documents fungal-host symbiosis as a mechanism for salt tolerance in plants (Rodriguez and Redman, 2008), but no equivalent framework has been proposed for mammals.

The Saline Oscillation Hypothesis presented here is, to the author's knowledge, the first to propose that cyclical drinking water salinity in the East African Rift Valley served as the environmental substrate for an ECS-mediated fungal-mammalian co-evolutionary program,

and that this program, preceded by a phytocannabinoid-mediated social flywheel and accelerated by the emergence of language, constituted the specific mechanism driving the evolutionary events Maslin and colleagues identified but left mechanistically unexplained.

In addition to the saline oscillation mechanism itself, this paper presents several novel contributions:

First, the synthesis of existing peer-reviewed evidence on *C. albicans* cross-kingdom signaling, host receptor interactions, and immune modulation into a unified framework that positions *Candida* not as an opportunistic pathogen but as the apex coordinator of the mammalian internal ecology. The individual findings cited in Section 5 are published and available. Their assembly into a coherent functional description of positional authority within the host microbiome has not been previously attempted.

Second, the effector hypothesis for farnesol function: a reinterpretation of farnesol's role from morphological self-regulation (the prevailing model since 2001) to a multi-target effector molecule whose morphological effects are a byproduct of broader environmental management. The twenty-two-year absence of an identified farnesol receptor in *C. albicans*, treated in the existing literature as an unresolved problem, is reinterpreted here as consistent with the effector model rather than paradoxical within it.

Third, the phenobarbital-colony distribution hypothesis: a proposed explanation for the variable anatomical geography of phenobarbital-associated mucosal ulceration across patients, based on differential density of the resident commensal *Candida* population rather than direct drug toxicity. This hypothesis is supported by two documented iatrogenic activation events in the longitudinal case study (Craddock, 2013; 2026b) and by published case reports.

Fourth, the reinterpretation of single-cell bet hedging behavior in *C. albicans* (first characterized at the transcriptomic level in fungi by Dumeaux et al., 2023) within the context of a co-evolutionary symbiont framework rather than a pathogen resistance framework. The original characterization described cytoprotective programs enabling drug tolerance. The present paper interprets the same data as evidence of an architectural survival system consistent with 200 million years of co-evolutionary refinement.

1. Introduction

The endocannabinoid system (ECS) is among the most ancient and conserved signaling systems in mammalian biology, with enzymatic components traceable to the unicellular common ancestor of animals and plants approximately one billion years ago (Elphick, 2012; McPartland et al., 2006). CB1 and CB2 receptors are present in all vertebrates and in chordate invertebrates such as the sea squirt *Ciona intestinalis* (Elphick et al., 2003), while endocannabinoid ligands including anandamide and 2-arachidonoylglycerol (2-AG) have been detected in organisms as primitive as *Hydra vulgaris* (De Petrocellis et al., 1999). The system maintains homeostasis across virtually every mammalian organ system, governing

pain perception, mood, appetite, immune function, metabolism, and reproduction (Acharya et al., 2017; Pandey et al., 2009).

Candida albicans, the most prevalent fungal commensal of the human mycobiome, is an obligate symbiont with no known environmental reservoir (Ost and Round, 2023; Kumamoto, 2011). Recent work has demonstrated that *C. albicans* colonization of the mammalian gut directly modulates the endocannabinoidome, producing specific changes in anandamide and 2-AG levels that alter hypothalamic-pituitary-adrenal (HPA) axis function and behavior (Markey et al., 2020). Separately, the black truffle *Tuber melanosporum* has been shown to produce anandamide and express the major ECS metabolic enzymes NAPE-PLD, FAAH, DAGL, and MAGL, suggesting that fungal endocannabinoid production is phylogenetically ancient and may predate the evolution of cannabinoid binding receptors themselves (Pacioni et al., 2015).

The *Mammalia candidus* hypothesis (Craddock, 2026a) proposed that the conserved mammalian ECS represents an interface layer selected for and refined through co-evolution between fungal symbionts and mammalian hosts across approximately 200 million years. The present paper extends this framework by identifying a specific environmental driver, the cyclical salinity oscillations of East African Rift Valley lakes during the Plio-Pleistocene, and proposing a three-part co-evolutionary model (the “evolutionary trinity”) involving the fungal symbiont, host physiology, and social structure, with the social component initiated by communal phytocannabinoid use and accelerated by the emergence of language. We designate the symbiont-active hominid phenotype *Homo candidus*, not a separate species, but a functionally distinct physiological and cognitive state produced by full activation of the co-evolutionary program.

While the ECS remains the primary documented interface between symbiont and host, evidence presented in Section 5 demonstrates that the signaling capacity of *C. albicans* extends substantially beyond the cannabinoid receptors, encompassing nuclear transcription factors, ion channels, neurotransmitter receptors, cholinergic signaling, and immune cell differentiation pathways. The ECS is the trunk of this signaling architecture. The broader receptor landscape is the canopy.

2. Geological and Paleoclimatic Context

2.1 The East African Rift Valley as Cradle of Hominid Evolution

The East African Rift System (EARS) is an active continental rift zone extending over thousands of kilometers from the Red Sea to Mozambique (Chorowicz, 2005). The region between Lake Turkana and Lake Natron is designated the “Cradle of Mankind” based on the density and significance of hominid fossil discoveries, including *Australopithecus afarensis* (“Lucy,” ~3.2 Ma; Johanson and White, 1979), *Homo erectus* (KNM-WT 15000 “Turkana Boy,” ~1.6 Ma; Brown et al., 1985; Walker and Leakey, 1993), the Lomekwi stone tools

(~3.3 Ma; Harmand et al., 2015), and *Paranthropus boisei* (“Nutcracker Man,” ~1.75 Ma; Leakey, 1959).

At Dalol, approximately 100 km north of the Afar Triple Junction, the rift floor contains a 5,000-meter-thick layer of evaporite salt deposits accumulated over the past four million years (Ebinger et al., 2000). The Eastern Rift lakes including Turkana, Magadi, Natron, Nakuru, and Elmenteita, are hydrologically closed basins with no outlet to the sea, resulting in high mineral content as evaporation concentrates dissolved salts (Britannica, “East African lakes”). Lake Magadi and Lake Natron are hypersaline soda lakes enriched in Na^+ , K^+ , Cl^- , CO_3^{2-} , and HCO_3^- (Deocampo and Renaut, 2022).

2.2 Pulsed Climate Variability and Lake Salinity Cycling

Maslin et al. (2014) established the “pulsed climate variability hypothesis,” demonstrating that the long-term aridification of East Africa was punctuated by episodes of short, alternating periods of extreme humidity and aridity. These pulses produced the rapid appearance and disappearance of extensive deep-water lakes within the EARS, driven by precession-forced changes in the precipitation-evaporation regime (Trauth et al., 2005; Kingston et al., 2007; Wilson et al., 2014).

During humid periods, rift lakes expanded, deepened, freshened, and in some cases overflowing into adjacent drainage systems (e.g., paleo-Lake Turkana overflowing into the Nile; Junginger and Trauth, 2013). During arid intervals, lakes contracted, becoming hydrologically closed, shallow, and progressively more saline and alkaline as evaporative concentration increased (Lyons et al., 2015; Scholz et al., 2007). The continuous 1.3-million-year sedimentary record from Lake Malawi documents 24 such severe dry periods with lake-level drops exceeding 200 meters (Lyons et al., 2015).

Critically, these salinity oscillations were not gradual. Wilson et al. (2014) demonstrated millennial-scale cyclicity (1,400–1,700 year periods) within the Baringo-Bogoria basin between 2.70 and 2.55 Ma, indicating that hominids in the region experienced transitions between freshwater and saline drinking water sources on timescales well within the range of adaptive physiological and behavioral response.

2.3 Temporal Correlation with Hominid Evolution

Shultz and Maslin (2013) demonstrated that hominid speciation events, changes in brain size, and dispersal events are statistically linked to the occurrence of ephemeral deep-water lakes in the EARS. The significant hominid speciation and brain expansion event at approximately 1.8 Ma, coincident with the emergence of *Homo erectus* and with the occurrence of “highly variable, extensive, deep-water lakes” (Maslin et al., 2014). The Turkana Basin, where many key fossils were found, dried out faster than the rest of Africa, forcing earlier adaptation to open, arid environments with periodically saline water sources (Turkana Basin Institute, 2021).

2.4 *Candida* Evolutionary Divergence and the Co-Evolutionary Timeline

The evolutionary history of the *Candida* clade provides independent temporal evidence consistent with the Saline Oscillation Hypothesis. *Candida parapsilosis* diverged from a last common ancestor with *C. albicans* approximately 70 Ma, coincident with the K-Pg extinction event and the explosive diversification of mammals (Butler et al., 2009; Nobile et al., 2021). This timing is consistent with the *Mammalia candidus* framework: as mammalian hosts diversified, their fungal symbionts co-diversified.

The divergence of *C. albicans* from its closest relative, *C. dubliniensis*, occurred more recently but remains imprecisely dated. The literature describes the split as occurring “relatively recently in evolutionary time” (Sullivan et al., 2005), with genome-wide nucleotide identity of 80–90% between the two species (Jackson et al., 2009). The critical observation is what happened after the split: *C. albicans* expanded gene families associated with host interaction and virulence (SAP, ALS, and IFF families), while *C. dubliniensis* underwent reductive evolution and widespread gene loss/pseudogenization that diminished its capacity to manage host physiology (Jackson et al., 2009; Thompson et al., 2021). This is not random drift; it is directional selection. *C. albicans* was being selected for deeper host integration while *C. dubliniensis* was not.

If the *C. albicans* / *C. dubliniensis* divergence occurred during the Plio-Pleistocene (~2–5 Ma), it would coincide precisely with the onset of salinity oscillations in the EARS, and the divergent evolutionary trajectories would have a clear explanation: *C. albicans* was under selection pressure to manage host perfusion and electrolyte balance during saline stress, driving the expansion of host-interaction gene families. *C. dubliniensis*, not under this pressure, shed the genes it did not need.

Additionally, atypical *C. albicans* strains isolated from vaginal specimens of Angolan women form a monophyletic group that may represent “an early stage of speciation” (McManus et al., 2008). The observation of ongoing *Candida* diversification in African populations, the geographic region of the proposed co-evolutionary origin, is consistent with the hypothesis that the selective pressures described here remain active.

3. The Pre-Linguistic Social Flywheel

3.1 Cannabinoid Discovery Before Salinity Oscillations

Cannabis sativa evolved approximately 28 million years ago on the eastern Tibetan Plateau (McPartland et al., 2019). Phytocannabinoid-producing plants were present in the environments accessible to hominid populations long before the Plio-Pleistocene salinity oscillations intensified. The discovery that certain plants produce psychoactive effects when consumed does not require language, agriculture, or sophisticated cognition. Instead, it requires only foraging and repetition.

THC (Δ^9 -tetrahydrocannabinol) is a direct CB1 and CB2 agonist (Pertwee, 2008) that activates the same receptor system through which the fungal symbiont communicates with the host. For a hominid already carrying *Candida* as a commensal and already possessing a functional ECS, the effects of phytocannabinoid consumption would be immediate: anxiolysis, mild euphoria, enhanced social bonding, reduced aggression, and appetite stimulation. In a host with an established symbiont relationship, these effects would be intensified, because the ECS interface is already upregulated by the symbiont's endogenous signaling.

3.2 The Social Bonding Effect

The behavioral effects of CB1 agonism are well-characterized: reduced aggression, increased prosocial behavior, enhanced appetite, and attenuated stress response (Lutz et al., 2015). A hominid group in which individuals communally consume phytocannabinoids would exhibit stronger social cohesion, less intra-group violence, and more cooperative behavior. These are precisely the traits required for the social leg of the evolutionary trinity.

This requires only that a group of hominids found something that made them feel good and pursued it together. The archaeological evidence for pre-linguistic communal behavior, cooperative foraging, group tool-making (Lomekwi, 3.3 Ma; Harmand et al., 2015), and social group structures in *A. afarensis*, confirms that hominids were capable of this level of social organization before language emerged.

We propose that the social flywheel began here: communal phytocannabinoid use → reduced aggression → stronger social bonds → more cooperative group behavior → better collective survival. Critically, this flywheel had an epigenetic dimension. THC exposure produces heritable DNA methylation changes in both sperm and somatic tissues, affecting genes involved in neurodevelopment, immune regulation, and synaptic plasticity (Szutorisz and Hurd, 2016; Schrott et al., 2020; Murphy et al., 2018). These methylation changes are transgenerational. Offspring of THC-exposed parents inherit altered epigenetic marks at genes including *DLGAP2* (a neurodevelopmental gene implicated in autism spectrum phenotypes) without direct exposure themselves (Schrott et al., 2020). Endocannabinoid signaling cascades mediated via CB1 and CB2 receptors regulate cellular functions through multiple epigenetic modifications including DNA methylation, histone methylation (H3K4me3, H3K9me2), and non-coding RNA networks (Szutorisz and Hurd, 2016). In the context of the pre-linguistic flywheel, communal phytocannabinoid use would not merely produce transient behavioral changes; it would inscribe those changes epigenetically, biasing offspring toward enhanced ECS sensitivity, increased prosocial behavior, and deeper symbiont integration. Each generation of communal cannabinoid use ratcheted the epigenetic baseline, reinforcing the social structure that produced it.

This established the social leg of the trinity before the salinity oscillations deepened the symbiont relationship and before language accelerated the entire system. Two of the three legs, 1) the fungal symbiont (present as a commensal), and 2) the social structure (initiated and epigenetically reinforced by the cannabinoid flywheel), were in place before the environmental driver activated the full program.

3.3 Continuity Through the Salinity Period

Once the salinity oscillations began deepening the symbiont's integration (~2.7 Ma onward), the social flywheel did not stop; it accelerated. The same plant that had promoted peaceful communality now also served a pharmacological function: supporting individuals undergoing the physiological stress of SIADH-type events, easing the transitional stages between phases of the symbiont's program, and enhancing the cognitive clarity windows that would eventually become transmissible with the emergence of language. The flywheel spans the entire timeline, from pre-linguistic social bonding through the full activation of the trinity and into the Neolithic cultivation period.

4. The Saline Oscillation Mechanism

4.1 The Mechanistic Sequence

We propose that the cyclical salinity oscillations in East African Rift Valley drinking water sources activated and progressively deepened the ECS-mediated co-evolutionary relationship through the following mechanistic sequence:

Step 1: Saline acclimation. During arid periods, hominid populations drinking from concentrating lakes acclimated physiologically to elevated electrolyte intake, predominantly sodium. Renal sodium handling, blood volume, and osmotic set points adjusted over generations to the higher baseline.

Step 2: Freshwater disruption and SIADH-type events. When humid periods returned and lakes freshened, populations acclimated to saline water experienced rapid electrolyte dilution. This is the physiological equivalent of a modern human drinking distilled water. For a system calibrated to higher electrolyte concentrations, freshwater intake produces dilutional hyponatremia and triggers SIADH-type antidiuretic hormone responses: water retention, reduced urine output, and electrolyte imbalance. The disruption is proportional to the delta between the system's calibrated salinity and actual intake, not to the absolute salinity level.

Step 3: Symbiont advantage. Under conditions of electrolyte stress, a fungal symbiont capable of modulating host perfusion, blood volume, and electrolyte conservation through the ECS gained decisive selective advantage. The host carrying a more integrated *Candida* population, one that could signal through endocannabinoid pathways to manage vasoconstriction, sodium retention, and fluid distribution, survived the freshwater transitions better than hosts without this integration.

At the molecular level, the symbiont's advantage may be mediated through epigenetic modification. Salinity stress in vertebrates produces distinct epigenetic responses: in the half smooth tongue sole (*Cynoglossus semilaevis*), low salinity exposure alters DNA methylation patterns and gene expression of growth-related genes in the liver (Li et al., 2017), and histone modification (H3K4me3) directly regulates dozens of differentially

expressed genes under salinity change (Zhang et al., 2022). DNA methylation changes under salinity stress have been shown to regulate osmoregulatory and immune-related genes across both immediate and transgenerational timescales in fish (Metzger and Schulte, 2018). In the context of the Saline Oscillation Hypothesis, *Candida*-mediated ECS signaling during salinity stress episodes could drive methylation changes in host genes governing electrolyte handling, vascular tone, and immune modulation. These changes would persist epigenetically across generations, ratcheting the co-evolutionary relationship deeper with each oscillation cycle without requiring genetic mutation.

Step 4: Behavioral agency. The symbiont, communicating through ECS signaling, drove host behavioral adaptations: fluid withholding to conserve electrolytes, salt-seeking behavior, dietary shifts toward sodium-rich foods, and, critically, sustained long-distance running. The “runner’s high” is mediated by endocannabinoid signaling (anandamide and 2-AG), not endorphins as previously assumed (Fuss et al., 2015). In a host with deeper symbiont integration, the ECS response to running would be intensified. Running thus served a dual function: survival strategy (persistence hunting, foraging range expansion, predator avoidance) and pharmacological maintenance of the ECS tone the symbiont requires. The symbiont benefits from the host running because it elevates the same signaling molecules the symbiont uses endogenously.

Step 5: Brain expansion as byproduct. The progressively deeper ECS integration required for perfusion management produced enhanced neuroplasticity, cognitive function, and pain modulation as byproducts. The brain did not expand because of dietary improvement alone; it expanded because the ECS interface, the oldest signaling system in mammalian biology, was being refined by the symbiont’s activity across thousands of oscillation cycles. Each cycle ratcheted the co-evolutionary relationship deeper, analogous to the punctuated equilibrium model (Eldredge and Gould, 1972).

Step 6: Language acceleration. The combination of enhanced ECS tone, exogenous cannabinoid support (continuing from the pre-linguistic social flywheel), and the cognitive clarity windows during late-stage transition produced the conditions under which proto-language became full language. The elder who could articulate insights became the most valuable group member, and the group that protected its elders received that transmission. Language did not create the trinity. Two legs were already in place, but language completed and massively accelerated the process.

This sequence places the social flywheel’s initiation before 3.3 Ma (pre-Lomekwi), the deepening of the symbiont relationship at approximately 2.7–1.9 Ma (the documented salinity oscillation window), and the full trinity (symbiont, host physiology, language-enabled social structure with cannabinoid support) all operational by approximately 1.55 Ma, consistent with the fossil evidence of *H. erectus* displaying Broca’s area asymmetry, cooperative hunting, long-distance running capability, and the first dispersal out of Africa.

4.2 Evidence for Sodium-Dependent Physiological Architecture

The longitudinal case study documented in Craddock (2022, 2026b) provides observational evidence that the symbiont's program is critically dependent on electrolyte and caloric homeostasis:

- Sodium cravings intensify during active phases of the condition, consistent with the body demanding substrate for perfusion maintenance
- Sugar cravings dominated earlier phases of the condition (pre-2014), consistent with the symbiont driving caloric intake during active growth and maintenance stages; these shifted to predominantly salt cravings as the program progressed to perfusion-dependent stages
- Peripheral vasoconstriction (cold extremities) occurs when sodium and volume are insufficient, centralizing blood flow to maintain core organ perfusion
- The original subjects in the historical cohort (described in the redacted source article) withheld urination during final phases specifically to conserve electrolytes. This is the same strategy as dietary sodium loading, targeting the same problem: maintaining the osmotic gradient that keeps fluid intravascular
- Dietary salt intake directly affects symptom severity, pain levels, and peripheral perfusion quality

The electrolyte-dependent architecture described above also renders the system vulnerable to iatrogenic disruption through pharmacological agents that alter the metabolic behavior of the resident fungal population. Section 5.1 documents two such events in the longitudinal case study involving phenobarbital exposure, which induces CYP450 enzymes shared between the host and *C. albicans*, triggering a metabolic fuel switch from glucose harvesting to host tissue invasion. The sensitivity of the symbiont's program to pharmacological perturbation is itself evidence that the program exists; a passive commensal would not produce acute, dose-dependent tissue damage in response to a sedative.

4.3 The Vascular Mechanics of the Perfusion System

The *Mammalia candidus* framework (Craddock, 2026a) and the longitudinal case study (Craddock, 2022, 2026b) describe a cardiac mechanism in which the right atrium generates suction during diastolic expansion, contributing to pituitary perfusion via a negative-pressure gradient. This suction mechanism operates in concert with additional vascular dynamics:

The inferior vena cava (IVC), returning blood from the lower body to the right atrium, can become constricted, whether through external compression, reduced blood volume, symbiont-mediated vascular tone changes, or alterations in heart rhythm that modify the diastolic suction cycle. Changes in cardiac rhythm, mediated through ECS signaling on the conduction system, alter the timing and magnitude of atrial expansion, directly governing

how much negative pressure is generated to draw blood through the IVC. The symbiont thus manages not only vascular tone but the suction pump itself. IVC constriction reduces venous return from the lower body, creating a pressure differential. Because cardiac output must equalize across all outlets (the heart cannot selectively pump more to one circuit), any obstruction or backup in the lower-body venous return creates a compensatory increase in flow velocity through the unobstructed path: the cerebral vasculature. This is a straightforward application of conservation of flow in a closed hydraulic system. Reduced IVC return increases the relative perfusion of the brain, where no equivalent obstruction exists.

The reversed pressure differential across the kidney, documented in the longitudinal case study as the mechanism by which the host maintained renal function for over 30 years despite progressive kidney compromise, operates within this same system. Reduced IVC flow alters the pressure gradient across the renal vasculature, and the symbiont's ECS-mediated control of vascular tone allows selective management of which organs receive preferential perfusion at any given time.

The complete system (cardiac suction, IVC dynamics, renal pressure reversal, selective perfusion management, and electrolyte conservation) constitutes a unified architecture. It does not require any novel cardiac anatomy; it operates on standard mammalian cardiovascular hardware. What distinguishes *Homo candidus* is not different equipment but different *management* of the equipment, directed by the symbiont through the ECS.

The survivability implications of this altered perfusion system are substantial. Preferential cerebral perfusion produces increased mental focus and sustained cognitive performance under conditions that would impair an unmanaged host. The ability to maintain consciousness and function through events analogous to pseudo-Addisonian crisis, or other acute adrenal insufficiency episodes that would cause syncope in a standard host, represents a significant survival advantage in an environment requiring sustained vigilance against predators and competitors. Enhanced pain tolerance, mediated through both the ECS and the altered perfusion dynamics, permits continued physical activity through injuries and transitional discomfort. Increased endurance, supported by the same ECS tone that maintains perfusion, extends foraging range, persistence hunting capability, and migratory capacity. The altered immune state, with enhanced phagocytic activity under symbiont management, reduces susceptibility to bacterial infections. Collectively, these traits (mental focus, crisis tolerance, pain suppression, endurance, and immune enhancement) increase individual survivability and group competitiveness during periods between transitions.

In computational terms, the symbiont functions as a co-processor. A standard mammalian host has one regulatory system, the autonomic nervous system, managing cardiovascular, immune, and metabolic functions. *Homo candidus* has two: the autonomic system and the symbiont's ECS-mediated signaling, both operating on the same physiological hardware simultaneously. This dual-controller architecture produces measurably superior regulatory performance. The longitudinal case study (Craddock, 2026b) documents one expression of this: during standardized workplace fitness testing, the subject recorded the fastest heart rate recovery time to baseline in the tested population, a metric that directly reflects the

efficiency of cardiovascular regulation during the transition from exertion to rest. The simplest explanation is that two regulatory systems managing the return to homeostasis outperform one. This co-processor model also explains the enhanced crisis tolerance: during an acute physiological stress event, the autonomic system may be overwhelmed, but the symbiont's parallel ECS signaling continues to manage perfusion and vascular tone, preventing the loss of consciousness that would occur in a single-controller system.

The system also introduces vulnerabilities. Puncture wounds and lacerations carry elevated risk because the altered vascular dynamics and reduced blood volume leave less margin for hemorrhage. However, progressive cellular apoptosis and tissue tightening, documented in the redacted source article and in the longitudinal case study (Craddock, 2026b), produce noticeably strengthened and toughened skin, partially offsetting this vulnerability. During certain phases prior to full apoptotic skin toughening, altered skin permeability creates sensitivity to osmotic and chemical exposure; the longitudinal case study documents adverse reactions to pool water contact during early phases when permeability remains elevated (Craddock, 2026b).

Transitional periods between phases and the final stage of the program produce a spectrum of pain that is among the most significant vulnerabilities of the *Homo candidus* phenotype. The longitudinal case study documents pain presentations ranging from burning skin, to deep muscular pain, to organ-specific pain (liver, kidney, pancreas), to pain localized in the nail beds of fingers and toes (Craddock, 2026b). Pain severity fluctuates with the phase of the program and can reach levels that temporarily prevent normal function. Nausea accompanies transitions and a brief period of the final phase, further reducing functional capacity during these windows. Hunger is nearly constant throughout the program. The metabolic demands of the symbiont's activity and the host's altered energy production require sustained caloric and electrolyte intake; however, during transitions, appetite suppression from nausea creates a dangerous conflict between metabolic need and the inability to eat. The longitudinal case study documents the necessity of external encouragement to eat during these periods (Craddock, 2026b). In a pre-modern social group, this maps directly onto a caregiving function: members of the group actively feeding and encouraging the transitioning individual, a behavior that would emerge naturally in a group already bonded through communal phytocannabinoid use and reinforced by the value the elder produces during clarity windows.

The symbiont's program thus presents an evolutionary trade-off: enhanced capability between transitions, increased vulnerability during them. The social structure of the trinity, the group protecting and feeding the individual during vulnerable phases, exists precisely to manage this trade-off. The redaction of the original research that first documented this architecture, treatment, and medical condition represents suppression. This suppression concerns not just a clinical curiosity, but knowledge concerning a human phenotype that may have been foundational to the development of civilization itself. Even without those implications, the loss to science has caused a multi-generation loss of scientific exploration into fungal research, and billions of dollars spent developing treatments that may ultimately be traced to systems defined herein. Such a decision is scientifically unforgivable and should be investigated. Ultimately, whoever is responsible

should have their authority brought into question. This author has seen the original science. It exists.

4.4 Dietary Generalism as Selection Criterion

Paranthropus boisei, recovered from Olduvai Gorge near Lake Natron (~1.75 Ma; Leakey, 1959), specialized in consuming tough, fibrous grasses and seeds, a closed dietary strategy. The *Homo* lineage, by contrast, maintained dietary generalism, consuming varied foods including meat, which requires cooperative hunting and broader ecological engagement (Turkana Basin Institute, 2021).

We propose that the symbiont selected for the open architectural platform. A dietary specialist offers a fixed nutritional environment; a generalist offers a variable one. A variable internal metabolic environment gives the symbiont more biochemical options for its ECS-mediated program. The *Homo* line's flexibility, via metabolic, behavioral, and social pathways, made it the superior host. *Paranthropus* rigidified and went extinct. *Homo* stayed open and deepened the partnership.

5. Beyond Opportunistic Pathogen: Cross-Kingdom Chemical Authority

5.1 Reframing the Organism

Candida albicans is conventionally classified as an “opportunistic pathogen,” an organism that causes harm when the host's defenses are compromised. This framing has shaped nearly all research into *Candida* biology for over a century. It is not wrong in a narrow sense: *C. albicans* can and does cause disease in immunocompromised individuals. But the classification obscures more than it reveals.

We argue that *Candida albicans* represents a uniquely integrative adaptive system within the current conceptual framework of host-associated microbiology, warranting reclassification of its functional role in human biology.

C. albicans is an obligate commensal with no known environmental reservoir, transmitted vertically from mother to child (Kumamoto, 2011; Ost and Round, 2023). It colonizes the gastrointestinal tract of 40–60% of healthy humans (Romo and Kumamoto, 2020). Recent work has demonstrated that *C. albicans* colonization confers measurable benefits to the host, including calibration of systemic Th17 immunity, protection against bacterial pathogens including *Clostridioides difficile*, and modulation of gut metabolic homeostasis (Peroumal et al., 2022; Shao et al., 2019). Alonso-Monge et al. (2021) describe colonization as a “double-edged sword,” a framing that itself acknowledges the organism provides benefit alongside risk. A purely pathogenic organism would not require the qualifier.

We characterize this operational capacity as a biochemical computer (Craddock, 2026b): an organism that does not respond to environmental challenges through a single adaptive pathway but maintains a continuously running portfolio of regulatory programs,

distributed across its population, drawing on confirmed molecular interactions with host receptors, competing microorganisms, and its own epigenetic architecture to recalculate its next operational state in a tenure-maximizing adaptive process. The term is not metaphorical. It describes the functional output of the signaling, sensing, and adaptive capabilities documented in the sections that follow.

Real-World Implications: Iatrogenic Symbiont Activation

The consequences of misunderstanding *C. albicans* as a simple pathogen are not theoretical. They are clinical and documented.

Phenobarbital, a barbiturate sedative introduced in 1911, is a potent inducer of Cytochrome P450 (CYP450) enzymes in mammalian liver tissue. *C. albicans* possesses its own functional CYP450 enzyme system, including CYP51 (lanosterol 14 α -demethylase, essential for ergosterol biosynthesis), CYP52 (fatty acid and alkane metabolism), and CYP56 (cell wall integrity). These fungal CYP450 enzymes share sufficient structural and functional homology with their mammalian counterparts that phenobarbital-induced enzyme upregulation is not confined to the host. It extends to the resident fungal population.

The theoretical consequence is a metabolic fuel switch. Under normal commensal conditions, *C. albicans* in the gastrointestinal tract harvests dietary glucose from the lumen. When CYP450 induction by phenobarbital upregulates the CYP52 family, which handles lipid and fatty acid metabolism, the organism gains enhanced capacity to process host-derived lipids and proteins. This metabolic shift is linked to morphological transition: the switch from yeast form (commensal, lumen-dwelling) to hyphal form (tissue-invasive, secreting aspartyl proteases and phospholipases to digest the protective mucin layer and penetrate epithelial tissue). The drug does not cause infection. It changes the operating instructions of an organism that is already present everywhere.

The longitudinal case study (Craddock, 2013; 2026b) documents three such activation events in a single subject:

1. At age 14, a single recreational dose of phenobarbital was followed within 12 hours by emergency appendectomy. The surgeon reported the appendix was completely ulcerated. The subject was hospitalized for five days as physicians could not explain the failure to respond to antibiotics, consistent with a fungal rather than bacterial etiology.
2. At age 26, a prescription for Donnatal (a combination drug containing a small amount of phenobarbital) for gastrointestinal symptoms produced, over several days, diffuse ulceration across the entire gastric mucosa. Endoscopy revealed small ulcerations covering 100% of the stomach lining. The gastroenterologist described it as “the stomach of a 70-year-old.” The subject was 26. The uniform distribution of ulceration across the full mucosal surface is consistent with simultaneous activation of a commensal population distributed throughout the stomach, not with focal infection or drug-induced erosion.

3. The acute dose-response relationship was further demonstrated when the subject, prior to a scheduled endoscopy and in significant pain, ingested several Donnatal tablets simultaneously seeking relief. Within thirty minutes, the subject experienced severe abdominal pain and passed an acholic (white) bowel movement. The endoscopy that had already been scheduled subsequently revealed white lesions covering the entire gastric mucosa. The temporal relationship between a bolus dose of phenobarbital, acute GI distress, and passage of visibly abnormal material is consistent with rapid, dose-dependent activation of the resident fungal population. The subject did not connect the Donnatal to the phenobarbital exposure from adolescence until a subsequent ER visit, where a GI cocktail containing phenobarbital produced immediate symptom escalation.

The subject did not connect the two events until a subsequent accidental re-exposure to phenobarbital (contained in an emergency room medication) produced immediate symptom escalation. Subsequent research at a medical library identified multiple published case reports of phenobarbital-associated mucosal ulceration at variable anatomical locations, with resolution upon drug withdrawal. This pattern is consistent with iatrogenic symbiont activation rather than direct drug toxicity.

Published case reports document severe mucosal ulceration following phenobarbital exposure at variable anatomical locations across patients: stomach in some, small intestine in others, colon in others (reviewed in drug-induced gastrointestinal disease literature). Phenobarbital-containing combination drugs carry prescribing labels that contraindicate use in patients with severe ulcerative colitis, gastric ulcer, and obstructive disease of the gastrointestinal tract, and warn that “diarrhea may be an early symptom of incomplete intestinal obstruction” (DailyMed, Belladonna/Phenobarbital). The labels acknowledge the gastrointestinal risk without identifying the mechanism. Notably, prescribing labels manage this risk through contraindication rather than explanation, advising against use in patients with pre-existing gastrointestinal conditions without identifying the mechanism by which the drug interacts with the gastrointestinal environment. The variable geography across patients is inconsistent with a direct drug toxicity mechanism, which would produce anatomically consistent damage. It is, however, consistent with activation of a distributed commensal population whose density varies by individual and by anatomical segment. The same chemical signal, received simultaneously by a geographically variable colony, produces damage wherever the colony is densest. The drug is the broadcast. The colony location determines the impact site.

What follows in this section reframes *C. albicans* not as a pathogen that occasionally behaves commensally, but as a systems-level coordinator of the mammalian internal ecology, an organism whose confirmed molecular capabilities position it as the emergent ecological regulatory influence via evolutionary selection, signaling authority within the host microbiome. The evidence presented is drawn entirely from peer-reviewed literature. What is novel is the assembly.

5.2 The Scope of the Signaling Network

Candida produces and secretes a library of bioactive metabolites numbering in the low hundreds based on current metabolomic profiling. Comprehensive two-dimensional gas chromatography has identified 126 volatile metabolites from *C. albicans* alone, distributed across acids, alcohols, aldehydes, hydrocarbons, esters, ketones, terpenic compounds, phenols, and sulphur compounds, representing a 70% increase over previously reported metabolites for the species (Perestrelo et al., 2020). Multi-omics studies using high-resolution mass spectrometry have identified 192 metabolites under controlled conditions (Gómez-Gaviria et al., 2023). These numbers represent what has been detected *in vitro*. The metabolite profile of *C. albicans* living inside a mammalian host, responding to host signals, immune pressure, variable nutrient availability, oxygen gradients, pH shifts, and co-resident microbiota, remains largely uncharacterized.

The primary signaling molecule characterized to date is farnesol (E,E-3,7,11-trimethyl-2,6,10-dodecatrien-1-ol), a sesquiterpene alcohol first identified as a eukaryotic quorum-sensing molecule in *C. albicans* by Hornby et al. (2001). Farnesol was the first quorum-sensing molecule discovered in any eukaryotic organism. Its effects, however, are not confined to intraspecific communication. Farnesol exerts confirmed, dose-dependent biological activity across three kingdoms of life: Fungi, Bacteria, and Animalia.

5.3 Fungal-to-Fungal Signaling

Farnesol produced by *C. albicans* inhibits growth and induces apoptosis in *Aspergillus nidulans* through a mechanism dependent on G-protein signaling, affecting mitochondrial function and reactive oxygen species production (Semighini et al., 2006). The compound inhibits cell wall integrity signaling in *Aspergillus fumigatus* (Dichtl et al., 2010) and is cytotoxic to *Saccharomyces cerevisiae*, *Penicillium expansum*, and *Botrytis cinerea* (Egbe et al., 2017). These effects require no physical contact between organisms. They are mediated entirely through extracellular chemical signaling. *Candida* does not consume or parasitize these competing fungi. It suppresses them chemically while occupying the same ecological niche.

5.4 Fungal-to-Bacterial Signaling

The cross-kingdom reach of *Candida*'s signaling extends to prokaryotes. Farnesol reduces the *Pseudomonas aeruginosa* quinolone signal (PQS) and its downstream virulence factor pyocyanin by approximately 72%, an effect replicated when *P. aeruginosa* is co-cultured with farnesol-producing *C. albicans* (Cugini et al., 2007). In mixed-species biofilms of *C. albicans* and *Staphylococcus aureus*, farnesol induces reactive oxygen species in the bacterium, upregulating drug efflux pumps that alter the bacterium's antibiotic susceptibility profile and effectively sensitizing *S. aureus* to antimicrobial compounds (Kong et al., 2017). These interactions are bidirectional: bacterial quorum-sensing molecules including *P. aeruginosa*-produced 3-oxo-C12-homoserine lactone suppress *C. albicans* filamentation at concentrations achieved in mixed-species biofilms (Hogan et al., 2004). The chemical negotiation is continuous and mutual, but *C. albicans* is the only

participant that simultaneously signals to bacteria, to competing fungi, and, as described below, to the mammalian host.

The cross-kingdom chemical reach described above operates primarily through small lipid-soluble molecules. A distinct but complementary modality, peptide mimicry, has been documented in other fungal systems and establishes the biological plausibility of peptide-based cross-kingdom manipulation in *C. albicans*.

The pathogenic yeast *Blastomyces dermatitidis* produces dipeptidyl-peptidase IVA (DppIVA), a close functional mimic of the mammalian ectopeptidase CD26. Like its mammalian counterpart, fungal DppIVA cleaves CC chemokines and GM-CSF, crippling monocyte recruitment, blocking phagocyte activation, and preventing reactive oxygen species production. Silencing the DppIVA gene restored immune function and curtailed virulence; addition of recombinant DppIVA to gene-silenced yeast restored immune evasion (Sterkel et al., 2016). This is the cleanest published demonstration that a fungal pathogen can produce a mammalian-mimicking peptidase as a deliberate immune manipulation tool.

In plant-fungal systems, cross-kingdom peptide mimicry is well-established. *Fusarium oxysporum* produces RALF-like peptides that are structurally identical to host plant signaling peptides and are recognized by plant receptors as genuine signals, activating nutrient uptake and immunomodulatory pathways (Masachis et al., 2016). A 2025 study in *Ustilago maydis*, the corn smut fungus, revealed a co-evolved peptide-GPCR sensing mechanism: the fungus secretes the protein Pit2, which is cleaved by host apoplastic proteases, releasing a peptide ligand that activates the fungus's own GPCR (Gpe1), signaling that host entry has occurred and promoting fungal proliferation (Krombach et al., 2025, bioRxiv). This represents a fungal organism using host enzyme activity as an environmental signal through a peptide intermediary.

Three independent examples across three fungal species and both plant and animal hosts establish that cross-kingdom peptide signaling is not hypothetical in fungal biology. *C. albicans*, with approximately 200 million years of mammalian co-evolution, 1,300 or more uncharacterized genes with no orthologs in other yeast species, and a confirmed peptide-processing machinery homologous to the mammalian prohormone convertase system, would be the anomaly if it were not engaging in peptide-based host manipulation. The question is not whether it does so, but through which of its uncharacterized genes and through which host receptors.

5.5 Fungal-to-Host Signaling: The Expanded Control Surface

The preceding sections of this paper describe the symbiont's interaction with the host primarily through the endocannabinoid system (ECS), with CB1 and CB2 receptors serving as the best-characterized interface layer for host-symbiont signaling integration. This remains the most extensively documented pathway of lipid-mediated physiological coupling. However, the ECS does not represent an isolated signaling module. It is one

branch of a broader lipid-derived regulatory architecture rooted in shared membrane biochemistry.

Arachidonic acid, an omega-6 polyunsaturated fatty acid embedded in membrane phospholipids, serves as a central precursor for both endocannabinoid synthesis and the prostaglandin/eicosanoid signaling pathways. The primary endocannabinoids, anandamide and 2-arachidonoylglycerol (2-AG), are generated from arachidonic-acid-containing phospholipid substrates, while prostaglandins arise from free arachidonic acid released from the same membrane reservoir through phospholipase-mediated cleavage. These pathways are not merely parallel outputs of a common precursor pool; they exhibit enzymatic and metabolic convergence. Cyclooxygenase-2 can directly oxygenate endocannabinoid intermediates, while endocannabinoid degradation regenerates arachidonic acid available for diversion into eicosanoid production. The ECS and prostaglandin systems therefore operate as partially coupled expressions of a shared lipid signaling economy.

Within this biochemical context, receptor-level signaling must be understood as the receptor-level signaling reflects underlying substrate-level coupling. CB1 and CB2 receptors are members of the larger G-protein-coupled receptor (GPCR) superfamily, comprising approximately 800 receptors encoded in the human genome and representing over 3% of all protein-coding genes (Fredriksson et al., 2003). Structural conservation across this receptor family implies that lipid-soluble ligands capable of engaging cannabinoid receptors may exhibit varying degrees of affinity across related GPCR targets. The ECS may therefore represent an early and well-characterized interface within a broader receptor landscape shaped by shared membrane-derived signaling substrates.

The ECS may be the original handshake between symbiont and host, but once an organism is producing lipid-soluble compounds that can dock with the seven-transmembrane architecture, the entire GPCR family becomes potentially accessible. The signaling capacity did not remain confined to two receptors across 200 million years of co-evolution, producing the ultimate survivor — a biochemical computer (Craddock, 2026b) continuously recalculating what moves might be required next. Instead, signaling capacity grew outward from the same structural foundation. CB1 and CB2 are the trunk. The broader receptor landscape is the canopy.

From an evolutionary systems perspective, the lipid signaling architecture is less accurately conceptualized as a linear pathway than as a branching network emerging from common biochemical roots. In this framework, the ECS functions as a central trunk, while prostaglandin-mediated inflammatory and vascular signaling represents a parallel branch derived from the same membrane substrate economy. The expansion of signaling capacity across this receptor landscape reflects the progressive elaboration of lipid-mediated regulatory mechanisms over evolutionary time growing outward from the same structural roots.

Farnesol alone, one compound from a library of hundreds, has been shown to interact with multiple classes of host receptor and signaling systems beyond the ECS:

Nuclear receptors. In 1995, Forman et al. identified a mammalian orphan nuclear receptor activated by farnesol metabolites, subsequently named the farnesoid X receptor (FXR). FXR directly regulates gene transcription governing bile acid metabolism, lipid homeostasis, glucose metabolism, and hepatic function. Farnesol also activates peroxisome proliferator-activated receptors (PPARs), nuclear receptors that regulate lipid metabolism, inflammation, and cellular differentiation. These are not membrane-level signals. They represent direct access to the host's transcriptional machinery.

Ion channels. Farnesol was identified by Rouillet et al. (1999) as an endogenous inhibitor of N-type voltage-gated Ca^{2+} channels in mammalian cells. Calcium signaling is foundational to virtually every cellular process, including cardiac conduction, a point of direct relevance to the cardiac architecture hypothesis described in Section 7. Farnesol is present in the human brain at measurable concentrations of 110–290 pmol/g (Rouillet et al., 1999).

Neurotransmitter receptors. Gc et al. (2023) demonstrated that farnesol acts as a positive allosteric modulator of γ -aminobutyric acid type A receptors (GABA-A), binding to the transmembrane neurosteroid site through a lipid pathway. GABA-A receptors mediate the primary inhibitory neurotransmission in the mammalian central nervous system and are the targets of benzodiazepines, barbiturates, and alcohol. This finding establishes a direct molecular pathway between a *Candida*-produced metabolite and the modulation of host consciousness, anxiety, and neurological function.

The incretin system. The GLP-1 receptor, a GPCR in the Secretin family, co-evolved alongside the ECS and demonstrates confirmed crosstalk with cannabinoid signaling pathways. Peroumal et al. (2022) demonstrated that *C. albicans* colonization of the murine gut measurably alters levels of GLP-1, GIP, insulin, and other metabolic hormones. The GLP-1 receptor is the target of the semaglutide and tirzepatide drug classes currently prescribed to tens of millions of patients for metabolic disease, generating hundreds of billions of dollars in market value. No published study has investigated what chronic GLP-1 receptor agonism does to the fungal symbiont ecology or how the symbiont adapts its signaling in response. This represents an intervention in an unmapped system, modulating a receptor whose relationship to the resident fungal ecology has never been characterized.

Immune modulation. Farnesol induces apoptosis in macrophages (Navarathna DH, Nickerson KW, et al. (2007)). Tyrosol, a second *C. albicans* quorum-sensing molecule, inhibits neutrophil reactive oxygen species production, disabling the oxidative burst that constitutes the primary fungicidal mechanism of these immune cells (Joo et al., 2010). Farnesol significantly impairs the differentiation of monocytes into dendritic cells, downregulating surface markers critical for antigen presentation including CD1a, CD83, CD86, and dectin-1, the primary β -glucan recognition receptor (Leonhardt et al., 2015). Dendritic cells generated in the presence of farnesol fail to induce proper T-cell responses and do not secrete the Th1-promoting cytokine IL-12. Critically, farnesol simultaneously activates innate immune markers on monocytes and neutrophils without enhancing actual fungal uptake or killing (Leonhardt et al., 2015). The immune system appears active. It does not clear the organism.

The immune-gut-brain axis. Current research positions farnesol as a messenger in the immune-gut-brain axis (Gates et al., 2026). In murine models of central nervous system inflammation, farnesol at doses of approximately 100 mg/kg demonstrated protective effects by reducing oxidative stress and proinflammatory cytokines. Farnesol upregulates TLR2 and downregulates TLR4 and TLR6 expression in oral epithelial cells exposed to *C. albicans*, modulating the primary molecular defense mechanisms at the epithelial barrier (Décanis et al., 2009). The molecular targets of farnesol, specifically FXR and voltage-gated calcium channels, are both intimately involved in immune homeostasis, positioning farnesol as a plausible metabolic mediator of crosstalk among brain cells, immune cells, intestinal barrier cells, and intestinal microbes (Gates et al., 2026).

The cholinergic system. Acetylcholine (ACh), the primary neurotransmitter of the parasympathetic nervous system and the vagus nerve, represents another confirmed signaling interface between *C. albicans* and the mammalian host. Unlike the farnesol-mediated interactions described above, where the organism produces a compound that acts on host receptors, the cholinergic interface is bidirectional: the host signals to the organism, and the organism's presence alters host cholinergic signaling.

C. albicans possesses a functional cholinergic receptor. The general muscarinic receptor agonist pilocarpine hydrochloride inhibits *C. albicans* biofilm formation and pathogenicity, a phenomenon reversed by the muscarinic antagonist scopolamine (Nile et al., 2018). Acetylcholine itself inhibits *C. albicans* biofilm formation both in vitro and in vivo, while also modulating the yeast-to-hyphal morphological transition in a context-dependent manner (Rajendran et al., 2015; A & Sm, 2018). This is the first confirmed instance of *C. albicans* possessing a receptor for a host neurotransmitter, in contrast to farnesol, where no receptor has been identified in the organism despite extensive searching.

The interaction extends beyond receptor signaling to metabolic interdependence. Acetylcholine is essential for the formation of the chitin wall characteristic of fungi, and *Candida* species contribute to host acquisition of choline, the precursor to acetylcholine synthesis (Chen et al., 2022). The organism is not merely sensing the host's cholinergic signaling; it is a participant in the host's choline economy, both consuming choline for its own structural needs and contributing to the host's choline pool.

The implications for host physiology are direct. The cholinergic anti-inflammatory pathway, a primary mechanism by which the host regulates immune responses, is mediated by acetylcholine released from efferent vagus nerve terminals. This acetylcholine interacts with the alpha-7 nicotinic receptor ($\alpha 7nAChR$) on proximal immune cells to downregulate localized inflammation (Rajendran et al., 2015). *C. albicans* infection in murine models significantly elevates acetylcholine levels in both brain and kidney tissue (2019 pyrimidine derivatives study). An organism with a functional cholinergic receptor, residing in the gut (the primary innervation territory of the vagus nerve), that also modulates host acetylcholine levels and participates in choline metabolism, has direct access to the parasympathetic nervous system and the vagal anti-inflammatory pathway.

The longitudinal case study (Craddock, 2026b) documents two distinct periods of choline-related supplementation spanning the full duration of the condition. Over approximately

two decades, the subject regularly consumed a choline-containing liver support supplement (LiverAid), initially motivated by concern for hepatic health given the metabolic stresses documented throughout the case, including ketoconazole-induced liver symptoms, dark urine, and digestive dysfunction. The subject came to recognize over time that the supplement functioned as a treatment, producing consistent relief of systemic tension and general symptom modulation, though the mechanism was not understood at the time.

In a much later stage of the condition, for a period of weeks in 2025, the subject experienced a distinct peripheral neurological symptom described as a vibrating sensation in the extremities, consistent in character with the pseudo-Addisonian crisis documented in 2018, though far lower in intensity. Direct choline supplementation via liquid drops resolved the vibrating sensation within seconds of administration. This temporal profile is not consistent with correction of a nutritional deficiency, which would require days to weeks. It is consistent with rapid restoration of cholinergic signaling in a system where the symbiont's metabolic demands on the shared choline pool produce a functional deficit in host acetylcholine availability. When the substrate is replenished, the signaling normalizes immediately.

Both observations are from a single subject and are anecdotal. They are, however, internally consistent with each other across a span of decades, and consistent with the documented role of *Candida* in host choline metabolism and the confirmed bidirectional cholinergic interface described above.

Anticancer selectivity. Farnesol induces apoptosis in various cancer cell lines, including lung, oral, and tongue carcinoma, by causing endoplasmic reticulum stress and mitochondrial dysfunction (Joo et al., 2009). Tumor cells are considerably more sensitive to farnesol-induced growth inhibition than normal cells; human primary T lymphocytes and monocytes are relatively resistant to the concentrations that kill leukemic cells. At supraphysiological concentrations, farnesol acts as a surfactant that accumulates in cell membranes, causing ion leakage and cell death. The preferential sensitivity of cancer cells, which carry defective signaling pathways secondary to genetic and epigenetic alterations, suggests that farnesol exploits the same pathway disruptions that make cancer cells malignant. An organism producing a compound that selectively eliminates cells with aberrant signaling while sparing cells with intact pathways is, in effect, performing quality control on host tissue.

5.5a The Peptide Signaling Layer: A Second Cross-Kingdom Channel

The signaling architecture described in the preceding sections operates primarily through lipid-mediated pathways: farnesol and the sesquiterpene library interact with GPCRs, nuclear receptors, ion channels, and neurotransmitter receptors through lipophilic docking. The endocannabinoid system itself is a lipid-signaling network. This lipid channel is the trunk of the signaling architecture, and we have argued it was the original handshake between symbiont and host. However, *C. albicans* also produces, processes, and imports peptides through a machinery that is not merely analogous to the mammalian peptide-processing system but directly homologous to it. This peptide layer constitutes a second, parallel cross-kingdom signaling channel, operating through different molecular classes,

different receptor targets, and different functional logic than the lipid channel, but running on shared enzymatic infrastructure that predates the mammalian-fungal divergence.

Shared peptide-processing machinery. *C. albicans* processes its Ece1 polyprotein through the Golgi-associated endoprotease Kex2p, a member of the subtilisin-family serine protease superfamily. Kex2p cleaves precursor proteins at dibasic lysine-arginine (KR) motifs to release multiple bioactive peptide products. The mammalian prohormone convertases PC1, PC2, and furin, the enzymes responsible for processing neuropeptide precursors, insulin prohormone, and other peptide hormone zymogens, possess catalytic domains directly homologous to Kex2p and were discovered by homology to the yeast enzyme (Richardson et al., 2018; Bader et al., 2008). The processing logic is identical: a precursor protein containing dibasic cleavage sites is proteolytically processed through sequential endoprotease and carboxypeptidase activity to yield mature bioactive peptides. In *C. albicans*, Kex2p performs the endoproteolytic cleavage and Kex1p removes the C-terminal arginine; in mammals, PC1/PC2 perform the analogous endoproteolytic step and carboxypeptidase E removes the C-terminal basic residues (Richardson et al., 2018).

This is not convergent evolution. It is conserved deep ancestry of the peptide-processing pipeline. The fungus and the mammalian host have been producing bioactive peptides through the same enzymatic grammar for the entire duration of their co-evolutionary relationship. An organism that already speaks the host's peptide-processing language does not need to evolve novel peptide-production machinery to interact with host peptide signaling. It needs only to evolve the sequences that, when processed through the shared machinery, produce peptides with the desired host-interaction profiles.

The Ece1 peptide panel. Kex2p processing of the 271-amino-acid Ece1 polyprotein produces eight discrete peptides, not one (Moyes et al., 2016; Richardson et al., 2018). Candidalysin (Ece1-III, positions 62–92), a 31-amino-acid cytolytic peptide toxin and the first such toxin identified in any human fungal pathogen (Moyes et al., 2016), has received the majority of research attention. However, the remaining seven Ece1 peptides are co-secreted during hyphal growth and have begun to yield functional data. A 2024 high-throughput yeast two-hybrid interactome screen (Lin et al., 2024) mapped the human protein targets of all eight Ece1 peptides and found that multiple non-candidalysin peptides, particularly Ece1-II and Ece1-V, interact with members of the leukocyte immunoglobulin-like receptor (LILR) family, specifically the inhibitory receptors LILRB1 through LILRB5. These receptors directly suppress immune cell activation. Functional enrichment of the shared interactors of Ece1-II and candidalysin revealed association with cell cycle regulation, Cyclin D-associated events in G1, and immune response-inhibiting cell surface receptor signaling pathways (Lin et al., 2024).

The Ece1 polyprotein is therefore not a toxin delivery system that incidentally produces byproducts. It is a coordinated peptide panel: one peptide for tissue invasion and membrane disruption (candidalysin), others for immune suppression through distinct receptor pathways (the LILR-interacting peptides), and potentially additional undiscovered functions among the remaining peptides. This architecture parallels mammalian prohormone precursors, which routinely produce multiple bioactive peptides with distinct functions from a single gene product (e.g., proopiomelanocortin yielding ACTH, α -MSH, β -

endorphin, and β -lipotropin). The parallel is not metaphorical. It runs on the same enzymatic machinery.

This multi-peptide architecture is consistent with the effector hypothesis proposed in Section 5.7. Candidalysin is the attention-grabber in pathogenesis research because it produces measurable tissue damage. But the quiet peptides, the ones interacting with immune-inhibitory receptors, may be performing the environmental management work that the effector model predicts: maintaining the conditions under which the symbiont's long-term program operates without triggering the inflammatory cascades that would destabilize the niche. The organism is not simply producing a weapon. It is producing a toolkit, with different peptides deployed for different aspects of host management, processed through the same Kex2p/Kex1p machinery in a single coordinated secretion event.

Candidalysin's expanding host target map. Recent work (2024–2025) has revealed that candidalysin's host interactions extend far beyond membrane lysis. The peptide binds glycosaminoglycans (GAGs) on epithelial cell surfaces, which promote its polymerization and facilitate membrane insertion, triggering calcium influx that activates the ESCRT-III membrane repair pathway (Lin and Filler, 2025). Inside the cell, candidalysin binds cyclin H (CCNH), a regulatory subunit of the CDK-activating kinase complex, activating it to inhibit double-strand DNA break repair (Lin et al., 2024). This has direct implications for the epidemiological association between *C. albicans* and oral and colorectal cancers, as CCNH expression is upregulated in gastrointestinal stromal tumors, breast cancer, esophageal squamous cell carcinoma, and brain tumors (Lin et al., 2024). In the lung, candidalysin binds GPIIb α , a subunit of the platelet receptor complex, inducing platelet activation and release of Dickkopf-1, which drives Th2 and Th17 immune polarization and reactive airway disease (Wu et al., cited in Lin and Filler, 2025). In epithelial cells, candidalysin induces EGFR ubiquitination and lysosomal degradation through a mechanism involving recruitment of Grb2, AP2M1, and HRS, effectively reprogramming host growth factor receptor trafficking (ASM, 2025).

Each of these interactions is peptide-to-host-receptor, distinct from the lipid-mediated farnesol pathway described in the preceding sections. The organism operates two parallel signaling channels: lipids for broad environmental tone-setting (ECS modulation, nuclear receptor activation, ion channel modulation, neurotransmitter receptor binding), and peptides for targeted action (tissue remodeling, DNA damage pathway hijacking, immune polarization, growth factor receptor manipulation). Two languages, one architecture.

Peptide transport capacity beyond commensal necessity. *C. albicans* encodes ten dedicated peptide transporters: two members of the PTR family (Ptr2 and Ptr22), which handle dipeptides and tripeptides, and eight members of the OPT family (Opt1 through Opt8), which handle oligopeptides up to at least eight amino acids in length (Dunkel et al., 2013; Reuß and Morschhäuser, 2006). This represents a substantial expansion relative to *Saccharomyces cerevisiae*, which encodes a single PTR family member. The SAP (secreted aspartyl proteinase) family provides the extracellular digestion component: SAPs degrade host proteins in the extracellular space, and the OPT/PTR transporters import the resulting

peptide fragments as nitrogen sources. The system constitutes a complete digest-and-import pipeline tuned for operation inside a mammalian host.

Opt1 was found to be remarkably flexible, transporting all tripeptides tested and even a dipeptide, a substrate class never previously attributed to the OPT family (Dunkel et al., 2013). Opt7 specifically transports glutathione (Desai et al., 2011), the host's primary intracellular antioxidant, an import function that represents theft of the host's redox defense molecule rather than nutritional acquisition.

The evolutionary significance lies in what happened when the system was removed. Dunkel et al. (2013) constructed a septuple mutant lacking all five major OPT transporters and both PTR transporters. These mutants could not grow on peptides or proteins as sole nitrogen sources. Yet they had no fitness defect in a mouse model of gastrointestinal colonization. The fungus survived on alternative nitrogen sources in the gut. This massive peptide transport apparatus is therefore not essential for commensal survival. It is maintained by selection for a function that gut colonization alone does not require.

Within the co-evolutionary framework, this excess capacity has at least two interpretations. First, it supports the later-stage protein substrate utilization described in the fuel priority hierarchy (Craddock, 2026a): host amino acids and structural proteins become primary substrates during chronic depletion and terminal phases, and the transport machinery required for that utilization must be maintained even when it is not currently in use. Second, and more speculatively, the peptide importers may function not only as nutrient uptake systems but as environmental sensors, sampling host-derived peptides, including peptide hormones and neuropeptide fragments, as signals indicating host physiological state. An organism with ten dedicated peptide importers, operating in the gut lumen where peptide hormones including GLP-1, CCK, and PYY are actively secreted by enteroendocrine cells, has the molecular hardware to read the host's peptide signaling environment. Whether it does so remains uncharacterized, but the hardware is confirmed.

Neuropeptide–fungal bidirectional signaling. Mammalian neuropeptides, including Substance P, neuropeptide Y (NPY), calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide (VIP), and somatostatin, all signal through GPCRs and play dual roles in fungal infection: they possess direct antimicrobial activity against fungi, but some also enhance fungal virulence by promoting adhesion, invasion, and immune evasion (Augustyniak et al., 2021). This bidirectional relationship falls under the emerging discipline of microbial endocrinology, the recognition that microbes do not passively endure host signaling but intercept and exploit it.

The structural overlap between neuropeptides and antimicrobial peptides is striking. Many neuropeptides share amino acid composition, amphipathic design, cationic charge, and size characteristics with classical antimicrobial peptides (Brogden et al., 2005). The host's neuropeptide defense system and the fungus's peptide import and processing apparatus therefore create a bidirectional peptide communication channel that has been under co-selective pressure for the entire span of mammalian evolution. The host fires antimicrobial neuropeptides at the fungus; the fungus imports peptides through its OPT/PTR

transporters; the fungus fires back with its own Ece1-derived peptide panel. The ECS model presented in this paper covers the lipid half of this dialogue. The peptide layer is the other half.

A neuroanatomical note connects this to the perfusion architecture described in Section 4.3. The hypothalamus and pituitary stalk are the primary exceptions to the blood-brain barrier; they lack the tight endothelial junctions that exclude blood-borne molecules from brain tissue (Brogden et al., 2005). These are also the brain regions where neuropeptide-mediated immune defense is most critical and where neuropeptide Y-producing cells are concentrated in the olfactory system and other barrier zones (El Karim et al., 2008). If the symbiont is managing pituitary perfusion through the suction mechanism described in this paper, it is operating in the precise anatomical zone where peptide-based host defense and fungal peptide signaling would intersect most directly. The hypothalamic-pituitary axis is not only the perfusion target; it is the peptide-signaling battleground.

5.5b Extracellular Vesicles: The Logistics of Coordinated Signaling

The preceding sections describe the organism's signaling repertoire: lipid-soluble compounds that dock with GPCRs, nuclear receptors, and ion channels (Section 5.5); peptides processed through shared Kex2/prohormone convertase machinery that modulate immune receptors, DNA damage pathways, and growth factor signaling (Section 5.5a). Each pathway has been characterized independently, in isolated compound-target experiments. The obvious question is how the organism deploys these signals in coordination inside a living host, where hundreds of metabolites must reach specific cell types in specific combinations at specific times. The answer, increasingly documented in the peer-reviewed literature, is extracellular vesicles.

The packaging system. Extracellular vesicles (EVs) are lipid bilayer-enclosed particles, ranging from 30 nm to over 1 μm in diameter, released by cells across all domains of life. They serve as export and delivery systems, carrying cargo that includes proteins, lipids, nucleic acids, and polysaccharides protected within the membrane envelope (Zarnowski et al., 2018). *C. albicans* produces EVs in both planktonic (free-living) and biofilm states. More than 20 fungal species are now known to produce EVs (Karkowska-Kuleta et al., 2025). Unlike free-floating secreted molecules, EV cargo is shielded from enzymatic degradation in the extracellular environment and can be delivered across cellular barriers that individual molecules cannot cross unaided.

Morphology-dependent cargo programming. The organism does not produce a single class of vesicle. Martínez-López et al. (2022) demonstrated that hyphal extracellular vesicles (HEVs) and yeast extracellular vesicles (YEVs) from *C. albicans* differ in size, biogenesis, protein diversity, and functional impact on the host. YEVs are larger (400–500 nm), carry primarily cell wall proteins, and serve cell wall maintenance functions; mutant sensitivity to cell wall-disrupting agents is rescued by addition of wild-type YEVs. HEVs are smaller (100–200 nm), carry six-fold greater protein diversity, include cytoplasmic proteins related to intracellular transport and the endosomal sorting complexes required for transport (ESCRT) pathway, and produce stronger effects on human immune cells than YEVs. Notably, HEVs carry an active 20S proteasome complex as cargo (Martínez-López et al., 2022), a finding whose functional significance in the host context remains unexplored.

Ninety-two percent of YEV proteins were also found in HEVs, but these shared proteins represented only 16% of the HEV cargo, indicating that the hyphal state produces a substantially expanded vesicle payload.

The morphological transition from yeast to hyphal form, the same transition governed by farnesol-mediated signaling described in Section 5.7, therefore changes not only the organism's physical form and tissue-invasive capacity but also the composition and functional profile of its vesicle-based delivery system. Commensal yeast-form cells send maintenance vesicles. Tissue-invasive hyphal cells send a weaponized and diversified payload. The shift in vesicle cargo is coupled to the shift in morphological program.

Candidalysin delivery. Noll et al. (2025) demonstrated that *C. albicans* biofilm EVs contain candidalysin and can permeabilize planar lipid bilayer membranes in a dose-dependent manner. Biofilm EVs were unable to directly damage oral epithelial cells at tested concentrations but were able to induce cytokine responses, including IL-1 α , IL-1 β , G-CSF, and GM-CSF. EVs collected from biofilms at 24 hours and 48 hours differed in both cargo composition and their capacity to activate epithelial cells, with earlier EVs delivering candidalysin to the membrane surface and later EVs activating cells through candidalysin-independent mechanisms (Noll et al., 2025). The temporal shift in cargo composition indicates that the organism's vesicle production is not static; it changes over the course of biofilm maturation, producing functionally distinct vesicle populations at different stages.

Community coordination. Zarnowski et al. (2021) used machine-learning analysis of cargo proteomic data from ESCRT-pathway mutants with vesicle production defects to systematically identify functional EV cargo proteins. Of 63 candidate gene products tested through constructed mutant and complemented strains, 17 displayed reduced biofilm matrix accumulation and antifungal drug resistance, and an additional 8 exhibited defects in adhesion or dispersion. Critically, the mutant phenotypes were rescued by addition of wild-type EVs, confirming that the functional effects derive from specific cargo rather than from the vesicle membrane itself. Biofilm EVs are compositionally distinct from planktonic EVs, with 34% of the proteome unique to the biofilm state (Zarnowski et al., 2018). The biofilm's defining trait, the protective extracellular matrix that confers drug resistance, is coordinated through vesicle-mediated delivery of matrix components.

This coordination extends across species. Zarnowski et al. (2022) demonstrated that a set of 36 common cargo proteins is shared among biofilm vesicles across five *Candida* species, including the emerging pathogen *C. auris*. Select cargo mutants showed conserved functional defects across species, and wild-type EVs from one species could complement cargo mutant phenotypes in another. The vesicle proteome endows *Candida* species communities with shared properties central to biofilm pathogenicity, enabling interspecies cooperation through a common vesicle language.

Host cell internalization. *C. albicans* EVs are internalized by human macrophage-like cells (THP-1) through macropinocytosis and phagocytosis (Karkowska-Kuleta et al., 2025). EVs and their cargo act as chemoattractants for blood-derived neutrophils, recruiting immune cells to the vicinity of the fungal population. However, the recruited neutrophils do not activate phagocytosis or neutrophil extracellular trap (NET) release in response to the EVs

(Karkowska-Kuleta et al., 2025). The vesicles attract without triggering the kill response. This is consistent with the immune modulation pattern described throughout Section 5: the immune system appears active but does not clear the organism. The EV-mediated recruitment without activation represents a vesicle-level implementation of the same strategy achieved molecularly by farnesol's activation of innate immune markers on monocytes without enhancing fungal uptake or killing (Leonhardt et al., 2015).

Bidirectional vesicle exchange. The vesicle channel is not unidirectional. Human oral mucosal epithelial cells produce EVs that suppress *C. albicans* growth, inhibit hyphal formation, and reduce mucosal invasion both in vitro and in a mouse model of oral candidiasis (Zhang et al., 2022). The host fires defensive vesicles at the fungus; the fungus fires cargo-loaded vesicles at the host. This bidirectional vesicle exchange constitutes a physical logistics channel for the molecular arms race described throughout Section 5, with each side packaging and delivering functional payloads to the other across cellular barriers.

Implications for the co-evolutionary framework. The signaling architecture described in Sections 5.3 through 5.5a, farnesol interacting with nuclear receptors, candidalysin binding platelet receptors, Ece1 peptides docking with immune-inhibitory LILRs, is presented in the literature and in this paper as individual compound-target interactions. Extracellular vesicles provide the mechanism by which these interactions are coordinated in vivo. The organism does not broadcast hundreds of compounds into the extracellular space and rely on diffusion to find the right targets. It packages curated multi-signal payloads into membrane-enclosed vesicles, loads different cargo depending on its morphological state and the maturation stage of its community, and delivers those vesicles to host cells that internalize them through defined uptake pathways. The combinatorial problem that the in vitro caveat (Section 5.6) identifies, how does the organism coordinate hundreds of compounds simultaneously in a living host, is at least partially resolved by the EV delivery system.

In the context of the Saline Oscillation Hypothesis, EVs represent the operational logistics of the symbiont's program. The ECS provides the signaling interface. The peptide panel provides targeted effectors. The vesicles deliver both, together, to the right cells, at the right time, in the right combination. An organism with this delivery capability does not need every molecule to find its target independently. It needs only to load the correct payload and release it. Two hundred million years is sufficient time to refine the loading program.

5.5c Small RNA Cross-Kingdom Signaling: The Third Channel

The signaling architecture described thus far operates through two molecular classes: lipids and peptides. Each functions through receptor-mediated interactions at the cell surface or within the cell's cytoplasmic receptor infrastructure. A third class of cross-kingdom signal, small non-coding RNA (sRNA), operates through a fundamentally different mechanism: direct interference with host gene expression at the transcript level. Unlike lipids and peptides, which modulate cellular behavior through receptor signaling cascades, sRNAs can silence specific host genes by hijacking the host's own RNA interference (RNAi) machinery.

Established precedent: fungal small RNAs silence host genes. The foundational demonstration of cross-kingdom RNAi as a fungal virulence mechanism was published by Weiberg et al. (2013) in *Science*. The aggressive plant pathogen *Botrytis cinerea* produces small RNAs (Bc-sRNAs) that are transferred into host plant cells during infection, where they bind to Arabidopsis Argonaute 1 (AGO1), the central component of the host's RNA-induced silencing complex (RISC), and selectively silence host immunity genes including mitogen-activated protein kinases (MPK1, MPK2), a cell wall-associated kinase (WAK), and an oxidative stress gene (PRXIF). *B. cinerea* mutants unable to produce these sRNAs (*dcl1 dcl2* double mutants) displayed reduced pathogenicity. Arabidopsis *ago1* mutants, unable to load the fungal sRNAs into RISC, exhibited reduced susceptibility to the pathogen. The mechanism is specific: the fungal sRNAs silence target genes through sequence complementarity, not through generalized toxicity.

Bidirectional RNA trafficking via extracellular vesicles. Cai et al. (2018) demonstrated in *Science* that the delivery mechanism for cross-kingdom sRNA transfer is extracellular vesicles. Arabidopsis cells secrete exosome-like EVs that accumulate at fungal infection sites and are taken up by *B. cinerea* cells. The host-derived sRNAs within these vesicles induce silencing of fungal genes critical for pathogenicity. The EVs are associated with tetraspanin proteins, which form membrane microdomains that may govern selective cargo loading. The sRNA traffic is bidirectional: the fungus sends sRNAs into the host to suppress immunity, and the host sends sRNAs into the fungus to suppress virulence. Both directions use vesicle-mediated delivery. This establishes EVs as the physical transport layer for cross-kingdom RNA interference, linking the vesicle biology described in Section 5.5b directly to gene-level regulatory warfare.

Wernecke et al. (2025) further demonstrated that different members of the Argonaute (AGO) protein family in *B. cinerea* act in bidirectional cross-kingdom RNAi during infection, with BcAGO2 specifically required for effective delivery of pathogen small RNAs into host cells. A fungal RNA-dependent RNA polymerase (BcRDR1) was identified as a novel pathogenicity factor required for cross-kingdom sRNA production (Porquier et al., 2023). The molecular machinery for cross-kingdom RNAi in fungal pathogens is increasingly well-characterized.

Animal parasite precedent: sRNAs modulate mammalian immunity. Cross-kingdom sRNA transfer to mammalian cells is not confined to plant systems. The gastrointestinal nematode *Heligmosomoides polygyrus* secretes exosomes containing microRNAs that are internalized by mammalian cells and suppress host innate immunity (Buck et al., 2014). This establishes that sRNA delivery from a eukaryotic parasite to a mammalian host, with functional gene-silencing consequences, is a demonstrated biological mechanism, not a theoretical extrapolation from plant pathology.

RNA cargo in fungal extracellular vesicles. Fungal EVs carry diverse RNA classes. A comprehensive review of fungal EV RNA content (Peres da Silva et al., 2022) documented that EVs from pathogenic fungi including *Candida* species contain mRNAs, tRNA-derived fragments, ribosomal RNA fragments, antisense RNAs, and small non-coding RNAs. In *Candida auris*, caspofungin treatment altered both the quantity and RNA content of secreted EVs, with tRNA-derived fragments (21–55 nucleotides) comprising the most

abundant non-coding RNA class, alongside antisense RNAs and mRNAs encoding translation, nucleosome, and cell wall functions (Peres da Silva et al., 2022). Differentially expressed transcripts in these EVs included QDR3, a drug transport regulator associated with biofilm formation and virulence in *C. albicans*, and MP65, encoding a cell wall mannoprotein crucial for biofilm matrix integrity. The RNA cargo is not random cytoplasmic leakage; it shifts in response to environmental conditions, suggesting regulated loading.

Peres da Silva et al. (2022) compiled evidence that exonic sRNAs contained in fungal EVs regulate carbohydrate, lipid, fatty acid, and amino acid metabolism; vesicle trafficking; signal transduction; protein folding; and nucleic acid biosynthetic processes within fungal populations. A recent study demonstrated that fungal EVs regulate gene expression governing pathophysiological attributes of *C. albicans* itself, confirming that EV-associated RNA is functionally active at minimum within the producing species.

The uncharacterized channel. Whether *C. albicans* EV-associated sRNAs silence specific genes in mammalian host cells has not been directly demonstrated. The individual components required for such a mechanism are each independently confirmed: *C. albicans* produces EVs containing RNA cargo; these EVs are internalized by human macrophages through macropinocytosis and phagocytosis (Karkowska-Kuleta et al., 2025); mammalian cells possess a functional RNAi machinery including AGO proteins capable of loading exogenous sRNAs; animal parasites have been shown to deliver functional sRNAs to mammalian cells via EVs (Buck et al., 2014); and cross-kingdom RNAi through fungal sRNAs is a demonstrated virulence mechanism in plant-fungal pathosystems (Weiberg et al., 2013). The mechanistic pathway from fungal cell to mammalian gene silencing exists. What has not been shown is that *C. albicans* uses it.

Evolutionary logic of the third channel. Small RNAs are not conscious signals, intentional communications, or hierarchical controllers. They are molecular regulatory noise that evolution harnessed. A tRNA fragment released in an EV that happened to reduce expression of a host immune gene would confer a survival advantage on the producing cell. Over evolutionary timescales, the loading of such fragments into EVs would become non-random, selected for regulatory impact rather than occurring by chance. This is the same logic by which the paper interprets farnesol's cross-kingdom activity (Section 5.7): the molecule was not designed to suppress competing fungi and modulate host immunity. Its effects were selected for because they stabilized the niche.

The three signaling channels, lipids, peptides, and small RNAs, operate on different timescales and at different levels of biological organization. Lipid signaling modulates receptor-mediated tone: the homeostatic set points of the ECS, immune surveillance sensitivity, vascular tone, and metabolic balance. Peptide signaling executes targeted actions: tissue remodeling, immune receptor engagement, DNA damage pathway manipulation. Small RNA signaling, if confirmed in the *C. albicans*-mammalian system, would operate at the deepest level: direct modification of host gene expression, tuning the host's own transcriptional output to favor the symbiont's program. Each channel acts on different timescales: seconds to minutes for receptor signaling, minutes to hours for peptide-receptor effects and downstream cascades, hours to days for gene expression

changes mediated by sRNA silencing. Together, they constitute a layered control architecture spanning from immediate physiological modulation to long-term transcriptional reprogramming.

Host-side surveillance. If fungal sRNAs or mRNAs enter host cells via EVs, they encounter host-side quality control systems that may function as barriers to cross-kingdom RNA interference. Hia et al. (2026) demonstrated that the RNA helicase DHX29 sits at the A-site entrance of the translating 80S ribosome and monitors aminoacyl-tRNA sampling, detecting nonoptimal codon usage and recruiting the GIGYF2/4EHP complex to suppress mRNAs enriched in nonoptimal codons. *C. albicans* uses a dramatically different codon usage bias from the human genome, including its well-documented CUG codon reassignment (serine rather than leucine). Any fungal mRNAs that enter host cells and reach the translational machinery would be flagged by DHX29's codon surveillance. DHX29 also moonlights as a co-sensor for MDA5-mediated innate immune signaling, enhancing MDA5 recognition of structured RNAs and triggering type I interferon responses (Zhu et al., 2018). A single host protein thus monitors both the translational fidelity and the immunological identity of cytoplasmic RNA, presenting a two-layer barrier: translational surveillance of codon optimality and innate immune detection of foreign RNA structure.

In the co-evolutionary framework, this host-side barrier predicts a symbiont counter-adaptation: evolutionary optimization of exported RNA sequences to pass both the DHX29 codon screen and the MDA5 structural screen. This is testable. Comparison of the codon usage profiles of *C. albicans* secreted and exported transcripts, particularly Ece1 and other transcripts detected in EV cargo, against the human codon optimality landscape should reveal whether these transcripts are more human-optimized than the remainder of the *Candida* transcriptome. If they are, this constitutes evidence of co-evolutionary selection at the codon level: the organism tuning its exported RNA to pass the host's quality control.

Internal RNA transport infrastructure. *C. albicans* already possesses a dedicated internal RNA trafficking system. Elson et al. (2009) identified a She3-dependent mRNA transport mechanism that selectively transports 40 mRNAs to yeast buds and to the tips of growing hyphae, where secretion is concentrated through the Spitzenkörper vesicle cluster. The cargo mRNAs have diverged substantially from those of *S. cerevisiae*, and many encode genes that contribute to hyphal development and host tissue invasion. The authors note that specific mRNAs can move in and out of transport control over evolutionary timescales, indicating that the RNA targeting system is evolutionarily plastic. An organism that already targets specific mRNAs to the subcellular location where secretory vesicles are produced has the molecular infrastructure to load specific RNAs into extracellular vesicles. The step from intracellular RNA targeting to extracellular RNA delivery is not a large one; it requires only that the She3-dependent or analogous cargo be routed to the EV biogenesis pathway rather than exclusively to internal translation.

5.5d Oxylin Mimicry: Prostaglandin Production and the Shared Arachidonic Acid Economy

The lipid signaling architecture described in Section 5.5 centers on farnesol, a sesquiterpene alcohol that interacts with host GPCRs, nuclear receptors, ion channels, and

neurotransmitter receptors. Farnesol is synthesized endogenously by *C. albicans* from the mevalonate pathway, using the organism's own metabolic precursors. A second class of lipid-mediated host manipulation operates through a fundamentally different supply chain: the organism takes a precursor from the host and manufactures a molecule structurally identical to one of the host's own inflammatory mediators, then deploys it to reshape the immune landscape in its favor.

Authentic prostaglandin production from host-derived substrate. Erb-Downward and Noverr (2007), using liquid chromatography–tandem mass spectrometry, demonstrated that *C. albicans* produces authentic prostaglandin E₂ (PGE₂) from arachidonic acid (AA). The mass spectrometric fragmentation pattern of the fungal product was identical to that of a purified PGE₂ standard, confirming structural identity rather than mere cross-reactivity. Maximal PGE₂ production occurred at 37°C in stationary-phase cultures, conditions mimicking the host internal environment. Earlier work by Noverr et al. (2001) had identified a PGE cross-reactive compound (PGE_x) in *Candida* supernatants that was biologically active on mammalian cells, and the mass spectrometric characterization confirmed that this compound is authentic PGE₂.

The biosynthetic pathway is unusual. *C. albicans* does not possess a cyclooxygenase (COX) homolog, the enzyme family responsible for prostaglandin synthesis in mammalian cells (Erb-Downward and Noverr, 2007). Yet PGE₂ production is inhibited by both nonspecific cyclooxygenase inhibitors and lipoxygenase inhibitors. A fatty acid desaturase homolog (Ole2) and a multicopper oxidase homolog (Fet3) were identified as playing roles in the biosynthetic process, with *ole2/ole2* and *fet3/fet3* mutants exhibiting reduced PGE₂ levels. The organism has evolved an independent enzymatic route to the same product that the host produces through COX enzymes. This is convergent biochemistry at the product level with divergent machinery at the enzyme level, a pattern consistent with selection for the end product's functional utility rather than conservation of the biosynthetic pathway itself.

Precursor acquisition from the host. *C. albicans* does not contain arachidonic acid as part of its endogenous fatty acid repertoire (Erb-Downward and Noverr, 2007). The organism obtains its AA precursor from the host. During infection, *C. albicans* causes the release of arachidonic acid from host cell membrane phospholipids, which then serves both as a carbon source for yeast growth and as the precursor for prostaglandin biosynthesis (Deva et al., 2000; Agarwal et al., 2014). Supplementation of *C. albicans* cultures with exogenous AA significantly increases PGE₂ production (Noverr et al., 2001). Biofilm-forming *C. albicans* produces substantially more prostaglandin than planktonic cells, and oxylinin production is upregulated during biofilm formation (Alem and Douglas, 2005; Erb-Downward and Noverr, 2007).

The supply chain is therefore: the organism damages host cell membranes (through candidalysin pore formation, SAP-mediated digestion, or physical hyphal penetration), arachidonic acid is released from the damaged membrane phospholipids, the organism imports it, and converts it into a molecule indistinguishable from the host's own primary inflammatory prostaglandin. The raw material comes from the host. The manufacturing is done by the fungus. The product is deployed back against the host's immune system.

Immune polarization through molecular mimicry. The immunological consequences of fungal PGE₂ production are specific and directional. PGE₂, whether host-derived or fungal, promotes Th2-type immune responses and suppresses Th1-type responses (Noverr et al., 2001; Kundu and Noverr, 2011). In the context of *Candida* infection, Th1 responses are protective and lead to fungal clearance, while Th2 responses are non-protective and promote chronic or disseminating disease (Noverr et al., 2001). The organism produces the exact molecule that shifts the host's immune response from the profile that would clear the infection to the profile that permits persistence.

Kundu and Noverr (2011) demonstrated this directly using dendritic cell immunization models. Bone marrow-derived dendritic cells pulsed with *C. albicans* yeast cells could protect mice against systemic infection. However, exposure to either host PGE₂ or fungal PGE₂ during the antigenic stimulation period abrogated the protective effect entirely. In the presence of hyphae, PGE₂ promoted Th2 cytokine production (IL-4, IL-10) and suppressed Th1 cytokine production (IL-12). The fungal PGE₂ was functionally interchangeable with host PGE₂ in blocking protective immunity. This is molecular mimicry in the most literal sense: the host's immune system cannot distinguish the fungal product from its own.

The broader biological activity of the fungal PGE₂ on mammalian cells includes inhibition of splenocyte proliferation, suppression of TNF α production, and stimulation of IL-10 secretion (Noverr et al., 2001). IL-10 is an anti-inflammatory cytokine that dampens immune surveillance. TNF α is a proinflammatory cytokine critical for antifungal defense. The organism's prostaglandin output simultaneously suppresses what would kill it and amplifies what protects it.

Autocrine morphological feedback. The fungal PGE₂ does not act exclusively on the host. Both fungal PGE₂ and synthetic PGE₂ enhance the yeast-to-hyphal morphological transition in *C. albicans* (Noverr et al., 2001; Noverr and Huffnagle, 2004). Mammalian eicosanoid inhibitors also inhibit *C. albicans* oxylipin production, morphogenesis, and biofilm formation (Noverr and Huffnagle, 2004; Erb-Downward and Noverr, 2007). The prostaglandin output thus serves a dual function: it modulates the host immune response externally and feeds back into the organism's own morphological program internally. The same molecule that suppresses host Th1 immunity promotes the hyphal form that enables tissue invasion. One product, two targets, coordinated effect.

Conservation across *Candida* species. Prostaglandin production from exogenous arachidonic acid is not unique to *C. albicans*. Toth et al. (2015) characterized the prostaglandin profiles of *C. parapsilosis* and *C. albicans* using HPLC-MS and found that both species synthesize PGD₂ and PGE₂ as their primary products, along with compounds from other prostaglandin classes (PGH₂, PGF₂ β , PGA₂). Agarwal et al. (2014) demonstrated that *C. tropicalis*, *C. glabrata*, and *C. parapsilosis* all produce PGE₂ from exogenous AA, with production enhanced during biofilm formation and in the presence of subinhibitory antifungal concentrations. Strydom et al. (2010) confirmed PGE₂ production in *C. dubliniensis* biofilms, the closest relative of *C. albicans*. The conservation of prostaglandin production capacity across the pathogenic *Candida* clade, using host-derived arachidonic acid as substrate, is consistent with selection for this capability as a host-interaction trait rather than an incidental metabolic byproduct.

The shared arachidonic acid economy and the endocannabinoid connection. This section's findings converge with the central argument of this paper through a single biochemical fact: arachidonic acid is the shared precursor for both the prostaglandin/eicosanoid pathway and the endocannabinoid system. The two primary endocannabinoids, anandamide and 2-AG, are both synthesized from membrane-bound arachidonic acid-containing phospholipids (Sugiura and Waku, 2002; Di Marzo, 2006). Prostaglandins are synthesized from free arachidonic acid released from the same phospholipid pool by phospholipase A₂. Moreover, COX-2 can directly oxygenate 2-AG to yield prostaglandin glyceryl esters (Di Marzo, 2006), and the hydrolysis of both endocannabinoids regenerates free arachidonic acid that can be diverted into eicosanoid production (Di Marzo and De Petrocellis, 2006). The two pathways do not merely share a precursor pool; they share processing enzymes and recycling intermediates.

The host's arachidonic acid pool therefore feeds three competing biosynthetic demands: the host's own prostaglandin/eicosanoid production (inflammation, vascular tone, immune regulation), the host's own endocannabinoid production (homeostatic regulation via CB1 and CB2), and the symbiont's prostaglandin production (immune polarization toward the non-protective Th2 profile, morphological feedback into the hyphal program). The organism does not merely interact with the ECS through receptor-level signaling, as described in Section 5.5. It competes directly with the host's endocannabinoid biosynthesis for shared arachidonic acid substrate. When the organism diverts host-released arachidonic acid into fungal PGE₂ production, that arachidonic acid is no longer available for anandamide or 2-AG synthesis.

This creates a metabolic triangle in which the organism can modulate both the inflammatory tone (through PGE₂ output) and the endocannabinoid tone (through substrate competition) of the local tissue environment simultaneously, using a single precursor it obtains by damaging host membranes. The ECS trunk described in this paper and the prostaglandin branch described here are not separate signaling systems. They are two outputs of a shared lipid economy that the organism has inserted itself into. The lipid signaling architecture is not a tree with independent branches. It is a root system fed by a common pool, and the organism sits at the junction.

Framework integration. The oxylinin capability adds a fourth mechanism to the organism's immune modulation toolkit, alongside farnesol-mediated dendritic cell suppression (Section 5.5), candidalysin-driven immune polarization (Section 5.5a), and the Ece1 peptide panel's LILR-mediated immune inhibition (Section 5.5a). Each operates through a different molecular class and a different receptor system. Farnesol suppresses via nuclear receptor activation and GABA-A modulation. Candidalysin polarizes through EGFR and platelet receptor engagement. The Ece1 peptides inhibit through LILR binding. Fungal PGE₂ shifts the Th1/Th2 balance through the same prostanoid receptors (EP1–EP4) that the host's own PGE₂ engages. Four molecular classes, four receptor systems, one coordinated outcome: an immune environment that appears active but does not clear the organism.

In the context of the Saline Oscillation Hypothesis, the organism's capacity to manipulate vascular tone through prostaglandin production is directly relevant to the perfusion

management architecture described in Section 4.3. PGE₂ is a potent vasodilator in most vascular beds and regulates renal blood flow, sodium handling, and renin release. An organism producing authentic PGE₂ from host-derived substrate has direct access to the vascular control systems that govern the electrolyte and perfusion dynamics at the center of the saline oscillation mechanism. The prostaglandin capability is not separate from the perfusion program. It is one of the tools by which the program operates.

5.5e Bioelectric Signaling: Ion Manipulation and the Electrochemical Interface

Section 5.5 documents that farnesol inhibits voltage-gated Ca²⁺ channels (Roullet et al., 1999), establishing that a single *C. albicans* metabolite can directly modulate host ion channel function. Section 5.5a describes candidalysin's pore-forming activity, which causes uncontrolled Ca²⁺ influx across the host cell membrane (Moyes et al., 2016). These individual interactions, however, exist within a broader context: *C. albicans* possesses a comprehensive suite of ion transport, pH manipulation, and electrochemical environment-engineering capabilities that, taken together, position it as an active modifier of the ionic landscape in which the host's own electrochemical machinery operates. In the context of the Saline Oscillation Hypothesis, where electrolyte dynamics and perfusion management are central to the co-evolutionary program, this ionic manipulation capability represents the most direct mechanistic interface between symbiont activity and the host's Na⁺/K⁺-ATPase-dependent physiology.

Active pH manipulation through two independent metabolic pathways. *C. albicans* modulates extracellular pH through at least two genetically distinct mechanisms. Vylkova et al. (2011) demonstrated that when amino acids serve as the carbon source, *C. albicans* catabolizes them and excretes the amino nitrogen as ammonia, raising extracellular pH from approximately 4 to 7.5 within hours. This process is regulated by the transcription factor Stp2, which controls amino acid permease expression through the SPS (Ssy1-Ptr3-Ssy5) sensor system. The ammonia is exported through the Ato family of transporters, which is significantly expanded in *C. albicans* (10 members) relative to non-alkalinizing species (Vylkova et al., 2011). Danhof and colleagues (2016) identified a second, genetically independent pathway: when carboxylic acids such as lactate, pyruvate, or α -ketoglutarate serve as the carbon source, *C. albicans* rapidly neutralizes acidic environments without ammonia release, without inducing hyphal morphogenesis, and through mutations distinct from those that impair the amino acid-driven pathway. Two independent metabolic routes converge on the same environmental outcome: pH neutralization.

Most recently, Chen et al. (2025) identified the transcription factor Dal81 as a previously unrecognized positive regulator of alkalinization that physically interacts with Stp2 to co-regulate a broad set of downstream target genes governing amino acid metabolism, extracellular pH modulation, fitness, and pathogenicity. The alkalinization program is not a single-gene response; it is a coordinated regulatory network with multiple transcriptional inputs.

Phagosomal pH neutralization. The pH manipulation capability extends to the most hostile intracellular environment the host can deploy. Vylkova and Lorenz (2014) demonstrated that phagocytosed *C. albicans* cells neutralize the acidic phagolysosome through amino acid-driven alkalinization. Wild-type cells fail to co-localize with acidophilic

dyes, indicating they occupy a neutral phagosome. Mutants lacking Stp2 remain in acidic phagosomes, cannot initiate hyphal morphogenesis, are killed at higher rates, and cause less macrophage damage. Pharmacological neutralization of the phagosome restored hyphal morphogenesis in the *stp2Δ* mutant, confirming that the pH change itself, not another Stp2 function, is the critical trigger for escape. The organism rewrites the pH of the compartment the host designed to kill it, and uses the pH change to activate the morphological transition required for escape.

Vylkova (2017) reviewed pH modulation as a general fungal virulence strategy, noting that *C. albicans* alkalizes at a rate unprecedented among human fungal pathogens, and that the most pathogenic *Candida* species possess the most expanded arsenals of amino acid transporters and ammonia exporters. The correlation between alkalization capacity and pathogenic success across the genus supports the interpretation that pH manipulation is not metabolic waste disposal but environmental engineering in service of the organism's program.

Potassium transport and competition with the host. *C. albicans* maintains intracellular potassium concentrations of 200–300 mmol/L and must compete with host cells for extracellular potassium, which is typically present at only a few mmol/L in host fluids (Ramos et al., 2022). The organism possesses a complex potassium transport network including high-affinity uptake transporters (Trk1, Trk2), an outward-rectifying K⁺ channel (Tok1) with a membrane topology distinct from all other known potassium channel classes (recently resolved at atomic resolution; BPS, 2026), Na⁺/K⁺-ATPase pumps (Ena21-22), and the Na⁺/H⁺ antiporter Cnh1, which exports potassium in addition to sodium (Kinclova-Zimmermannova et al., 2007). A vacuolar transient receptor potential (TRP) channel (Yvc1) mediates calcium and potassium transport between the vacuole and mitochondria, governing the interaction among oxidative stress response, vacuolar integrity, and mitochondrial function (Yu et al., 2014). Ion homeostasis is directly connected to morphogenesis, drug resistance, cell wall integrity, and invasive growth (Li et al., 2018).

The organism's potassium transport activity directly alters the local extracellular K⁺ concentration in its immediate environment. In tissue microenvironments where *C. albicans* density is high, whether in biofilms, in the gut lumen, or within the novel peritoneal compartment described in the longitudinal case study (Craddock, 2026b), the organism's collective potassium uptake reduces the extracellular K⁺ available to adjacent host cells. This is not theoretical: the organism requires 200–300 mmol/L intracellular K⁺ and extracts it from a medium containing only a few mmol/L. At sufficient fungal density, this creates a measurable K⁺ depletion zone around the colony.

Candidalysin as a bioelectric disruptor. The pore-forming toxin candidalysin (Section 5.5a) is not merely a cytolytic agent. Each candidalysin pore is a local short-circuit in the host cell's electrochemical gradient. Russell et al. (2022) demonstrated that candidalysin forms pores through a unique mechanism: the peptide self-assembles into octameric polymers and loops in solution before inserting into the membrane, producing stable pores that cause uncontrolled Ca²⁺ influx, release of cellular proteins, and critically, efflux of ATP from the host cell into the extracellular space (Ho et al., 2021; Russell et al., 2022). The calcium influx triggers matrix metalloproteinase activation, EGFR signaling, and cytokine

release (Moyes et al., 2019). But the ATP efflux is equally significant: it represents the host cell losing its energy currency directly into the environment where the organism can access it. Simultaneously, the unregulated ion flux through the pore collapses the transmembrane potential that the Na^+/K^+ -ATPase maintains at a cost of 30–70% of total cellular ATP production.

Convergence: creating the conditions for pump reversal. The Na^+/K^+ -ATPase is a reversible enzyme. Garrahan and Glynn (1966), in a foundational paper in *Nature*, demonstrated that by arranging sufficiently adverse concentration gradients for sodium and potassium across intact red blood cell membranes, the Na^+/K^+ pump can be driven backwards to synthesize ATP from ADP and inorganic phosphate. They noted that the free energy available to drive the pump forward under normal physiological conditions is approximately 3,000 calories per ATP, a narrow thermodynamic margin between forward and reverse operation. Robinson, Hall, and Dunham (1977) further characterized the reverse mode in resealed red cell ghosts, measuring ATP synthesis as a function of internal K^+ concentration. Schwarz and colleagues (1991) demonstrated in *Xenopus* oocytes that under conditions of reduced intracellular Na^+ and ATP (both below 1 mM) combined with extracellularly K^+ -free medium, the pump operates in reversed mode, pumping Na^+ into the cell and K^+ out. A recent comprehensive review confirms that each stage of the NKA cycle is reversible contingent upon substrate availability, and that under specific conditions, NKA can operate in the opposite direction, acting as an ATP synthase (Bhatt et al., 2024).

The conditions required for pump reversal are specific: reduced intracellular Na^+ , reduced intracellular ATP, and reduced or absent extracellular K^+ . The organism's documented capabilities converge on precisely these conditions. Candidalysin pores cause ATP efflux from the host cell, reducing intracellular ATP. The same pores permit unregulated ion flux, collapsing the Na^+ gradient. The organism's high-affinity potassium uptake competes with host cells for extracellular K^+ , creating local K^+ depletion zones. pH manipulation through ammonia excretion alters the proton gradient that drives the Na^+/K^+ -ATPase. Farnesol inhibits voltage-gated Ca^{2+} channels, modifying the calcium signaling that regulates pump activity. No single mechanism needs to flip the pump by force. The organism nudges the electrochemical landscape from multiple directions simultaneously, and the thermodynamic margin is narrow enough that the cumulative effect can tip the pump past the reversal threshold.

Implications of reversed pump operation. If the Na^+/K^+ -ATPase operates in reverse mode in affected tissues, the consequences extend beyond energy metabolism. In forward mode, the pump maintains the electrochemical gradient that every cell depends on for volume regulation, membrane potential, excitability, and secondary active transport. In reverse mode, these gradients collapse or invert. The pump, which normally consumes 30–70% of cellular ATP to maintain gradients, instead harvests the stored electrochemical potential energy of existing gradients to generate ATP. The ion gradients that the cell spent its lifetime building become a fuel reserve.

In a system where conventional mitochondrial ATP generation is compromised, whether by fungal interference with mitochondrial function, substrate depletion, or the metabolic shifts documented in the longitudinal case study (Craddock, 2026b), reverse pump

operation would represent an alternative energy generation pathway. The host is, in effect, carrying a stored fuel source in every cell's ion gradient that is not accessed under normal physiological conditions. The organism's ionic manipulation capabilities provide the mechanism by which this reserve could be tapped.

The downstream physiological consequences of reversed gradients in affected tissue would include altered cell volume regulation (cells that can no longer maintain their normal volume may shrink through water loss, consistent with the apoptotic volume decrease that precedes programmed cell death), changes in membrane potential affecting excitability and signaling in nearby cells, disruption of secondary active transport systems that depend on the Na^+ gradient (including glucose co-transporters, amino acid transporters, and neurotransmitter reuptake systems), and altered skin physiology in tissues where the epidermis is affected.

Epidermal implications of altered gradients. The human epidermis is a continuously regenerating tissue. New keratinocytes are generated by division of basal layer stem cells sitting on the basement membrane, with direct access to dermal interstitial fluid and capillary diffusion. Daughter cells are pushed upward through the spinous, granular, and cornified layers, progressively flattening, keratinizing, and undergoing programmed cell death as they rise. In normal skin, the outermost cornified layers desquamate at approximately the rate new cells are produced, maintaining a steady-state thickness. If reversed electrochemical gradients in the upper epidermal layers accelerate apoptotic volume decrease in keratinocytes that have not yet reached the normal desquamation stage, while the basal layer continues to generate new cells at its normal rate, the result is accumulation: apoptotic layers stacking faster than they shed, producing progressive thickening, tightening, and compression of the skin. The basal layer, sitting on the basement membrane with full access to interstitial fluids, remains the last layer to lose function and continues generating new cells from below, even as the layers above it are compressed by the accumulating stack.

C. albicans hyphae are documented to penetrate through all epidermal layers including the basal layer, with sequential expression of secreted aspartyl proteinases at each depth (Schaller et al., 1999). The organism adheres to live basal keratinocytes via interactions between fungal phosphoglycerate mutase (Gpm1) and epithelial cell vitronectin (Lopez et al., 2014). Melanocytes in the basal layer detect *C. albicans* through TLR4 and respond by increasing melanin production (Tapia et al., 2014). Notably, Lachat et al. (2022) demonstrated that *C. albicans* hyphae can traverse multiple host cells within trans-cellular tunnels without causing membrane damage at early stages, indicating that the organism can establish intracellular presence in the epidermis while leaving the tissue structurally intact. An organism that reaches the basal layer, adheres to its cells, and can tunnel through the layers above without destroying them has the positional access required to influence the ionic environment of the regenerative layer from within, while the consequences of that influence — altered gradients, accelerated apoptosis, layer accumulation — manifest in the tissue above.

The tissue-level changes predicted by this model — progressive skin toughening, compression, tightening, and episodic burning from disrupted ion gradients activating

epidermal nociceptors — are documented in the longitudinal case study (Craddock, 2026b).

Integration with the saline oscillation mechanism. The Saline Oscillation Hypothesis (Section 2) proposes that cyclical drinking water salinity in the East African Rift Valley created SIADH-type electrolyte disruption during freshwater transitions. The organism's documented ionic manipulation capabilities, active pH modulation, potassium competition, transmembrane pore formation, and calcium channel modulation, are the molecular tools by which the symbiont would manage host electrolyte balance during precisely these disruptions. An organism that can raise extracellular pH by four units within hours, compete for potassium at concentrations two orders of magnitude above the extracellular supply, neutralize the acidic phagolysosome of the immune cells sent to destroy it, and punch calibrated pores in host cell membranes to modify transmembrane ion flux does not need a novel mechanism to manage saline oscillation. It needs only to apply the ionic manipulation capabilities it already possesses to the electrolyte environment it already inhabits.

The Na^+/K^+ -ATPase reversal mechanism adds a further dimension: under the altered ionic conditions the symbiont creates, the host's primary energy-consuming ion pump can become an energy-generating one. In the context of the co-evolutionary program, this may explain how the host maintains function, including the cognitive clarity documented in the historical cohort and the longitudinal case study, during phases when conventional energy production is compromised. The organism is not destroying the host's ionic infrastructure. It is repurposing it.

5.6 The In Vitro Caveat

The extracellular vesicle system described in Section 5.5b provides a partial answer to the coordination problem: the organism packages multi-signal payloads into membrane-enclosed vesicles with morphology-dependent and temporally variable cargo. Nevertheless, a critical methodological note is required. Virtually all of the receptor-level and cross-kingdom interactions described above were characterized *in vitro*: isolated compounds tested against isolated targets in controlled media. The morphological suppression, the competing-fungi apoptosis, the immune cell manipulation, the GABA-A binding, the nuclear receptor activation were all demonstrated in the reductionist context of cell culture or defined assay systems.

Inside a living mammalian host, the situation is fundamentally different. *C. albicans* is producing hundreds of compounds simultaneously, in varying concentrations, in different tissue microenvironments with variable pH, oxygen tension, carbon sources, immune pressures, and co-resident organisms at every location. The metabolite profile shifts depending on whether the organism is utilizing glucose or lactate, whether it is in yeast or hyphal form, and what signals it is receiving from the local microbial community and host cells. The *in vitro* work demonstrates that the keys fit the locks. It does not reveal which

doors are being opened, in what order, in what combination, or in response to what local conditions.

No study has attempted to map the integrated, real-time metabolite-receptor interaction network of *C. albicans* operating inside a living host. The individual components are peer-reviewed and confirmed. The assembled system has never been observed. The field's tools are reductionist. The organism is not.

5.7 The Absent Receptor and the Effector Hypothesis

Despite twenty-two years of active research since Hornby et al. (2001), no farnesol receptor or sensor has been identified in *C. albicans* itself (Nickerson et al., 2023). Multiple receptors for farnesol have been characterized in the mammalian host (FXR, GABA-A, voltage-gated Ca^{2+} channels, PPARs) and confirmed effects have been documented in competing fungi and bacteria. The producing organism does not appear to detect its own primary signaling compound.

The prevailing interpretation of farnesol function since its discovery has been morphological self-regulation: as population density increases, extracellular farnesol accumulates and suppresses the yeast-to-hyphal transition, maintaining the population in yeast form (Hornby et al., 2001). This quorum-sensing model is well-supported experimentally. The morphological suppression is reproducible, dose-dependent, and specific to the E,E-isomer (Shchepin et al., 2003).

However, the quorum-sensing model accounts for only one of farnesol's many confirmed biological activities. The same molecule that suppresses filamentation in *C. albicans* also induces apoptosis in competing fungi (Semighini et al., 2006), downregulates virulence signaling in bacteria (Cugini et al., 2007), activates nuclear transcription factors in the mammalian host (Forman et al., 1995), modulates the primary inhibitory neurotransmitter system in the brain (Gc et al., 2023), blocks voltage-gated calcium channels (Roullet et al., 1999), and selectively induces apoptosis in mammalian cancer cells while sparing healthy tissue (Joo et al., 2009). If the primary function of farnesol were morphological self-regulation, the breadth and specificity of its cross-kingdom activity would be difficult to explain, and the absence of any identified receptor in the producing organism would remain paradoxical.

We propose that morphological suppression is not the primary function of farnesol but rather one consequence of a broader effector strategy. The yeast form is the dispersal and commensal form of *C. albicans*; the hyphal form is the tissue-invasive form. An effector molecule that simultaneously suppresses premature tissue invasion, suppresses competing microorganisms, modulates host immunity, and accesses host transcriptional and neurological signaling would produce the observed morphological effect as a byproduct of maintaining the conditions under which the symbiont's long-term program operates. The organism is not telling itself to stay small. It is maintaining the operational environment in which its program runs.

The cross-kingdom activity described in Sections 5.3 and 5.4 is consistent with this effector interpretation. *Candida* does not suppress competing fungi and downregulate bacterial

virulence factors out of altruism toward the host. It does so because a stable host with a predictable internal environment is an optimal resource. Competing fungal infections trigger inflammatory immune cascades. Bacterial virulence factors cause tissue damage. Both destabilize the niche the symbiont requires. The organism's first imperative is to feed, to metabolize, to persist, to exist commensally. To do that optimally, it requires environmental parameters within a tolerable range. The cross-kingdom signaling described here is not grand strategy. It is ecological housekeeping in service of the organism's primary interest: an undisturbed host.

Not all cells participate in this maintenance at all times. *C. albicans* populations exist across a spectrum of activity states. The majority of cells in an untreated population are in baseline metabolic states, feeding, dividing, existing commensally (Dumeaux et al., 2023). A subset maintains the local environment through the signaling mechanisms described above. Others lie dormant in tissue niches distant from active immune surveillance, metabolically quiescent, pre-positioned, persisting. These are the waiting cells: not managing, not feeding aggressively, simply enduring until conditions change. The organism does not need every cell to be an active coordinator. It needs enough coordinators to maintain the niche, and enough reserves to survive if the niche is disrupted.

5.8 Evolutionary Adaptability: The Biological Prepper

The sophistication of *C. albicans*'s signaling architecture raises the question of how such a system is maintained under environmental pressure. Recent single-cell transcriptomic work by Dumeaux et al. (2023), published in *eLife*, provides a striking answer.

Using nanoliter droplet-based single-cell sequencing, Dumeaux and colleagues profiled thousands of individual *C. albicans* cells from isogenic populations, genetically identical cells from a single colony. They found that *before any drug exposure*, the population already exhibited heterogeneous expression of cytoprotective programs. Different cells within the same colony were stochastically running different transcriptional programs: some upregulating efflux pumps, some reinforcing cell walls, some in alternative metabolic states. This is "bet hedging," the pre-positioning of diverse survival configurations against threats that have not yet arrived.

When antifungal drugs were applied, the surviving cells partitioned into distinct subpopulations, each with a unique survival strategy involving different regulatory programs. The organism did not mount a single response. It deployed a portfolio of responses, distributed across the population, with different cells pursuing different survival paths simultaneously. At two days post-treatment, a burst of chromosomal aberrations was observed: controlled genome destabilization, expanding the search space for novel genetic solutions. Once resistance was achieved, the genome restabilized (Dumeaux et al., 2023).

This reflects a pre-existing adaptive architecture shaped by evolutionary selection. The organism maintains standing diversity in the face of unpredictable threats, deploys distributed survival strategies under environmental pressure, undergoes regulated increases in genomic variability when prior adaptive states become insufficient, and

subsequently stabilizes genomic architecture as selectively favored configurations emerge. The biochemical computer does not predict its next move. It has already prepared for contingencies it has not yet encountered. Proactive diversification, shaped by prior evolutionary pressures, precedes the onset of specific selective events. Microbial regulatory architectures may encode evolutionary “memory” of environmental variability, producing population-level response distributions that resemble probabilistic anticipation of future stress. Observed diversification may reflect evolutionary encoding of historical environmental variability rather than de novo anticipation of novel stress. (Mitchell et al. (2009), Tagkopoulos et al. (2008))

Biological bet hedging is not unique to *Candida*. The mammalian adaptive immune system maintains a massive library of naive B and T cells, each pre-configured with a different receptor specificity generated randomly through V(D)J recombination, before encountering any pathogen. Plant species produce seeds with variable dormancy periods within a single generation, distributing germination across unpredictable growing seasons. Bacterial persister cells spontaneously enter dormant, antibiotic-tolerant states within genetically identical populations before any antibiotic exposure.

But none of these systems combine bet hedging with controlled genome destabilization, cross-kingdom chemical signaling, host receptor access, morphological tissue mobility, and immune surveillance management simultaneously. The individual elements exist elsewhere in biology. The combination, as far as current characterization reveals, is unique to *Candida*. In commensal terms, *C. albicans* occupies the ecological position of the organism that cannot be eradicated, ie. candida represents a globally entrenched commensal lineage whose eradication would require interventions incompatible with host survival or ecosystem stability. Not because it is optimized for any single threat, but because it is pre-adapted for persistence across the full spectrum of environmental contingencies. It does not predict what will happen next. It has already prepared for it. A 14.3-megabase genome encoding approximately 6,400 genes, a third of the human gene count, running the most complete non-sentient survival architecture in known biology.

The mechanistic basis of the standing diversity described above is epigenetic rather than genetic. *C. albicans* possesses a comprehensive chromatin modification toolkit: histone acetyltransferases (HATs), histone deacetylases (HDACs), and histone methyltransferases regulate the commensal-to-pathogen lifestyle switch, the yeast-to-hyphal morphological transition, and the white-opaque phenotypic switch through reversible post-translational modification of histone proteins (Sagar et al., 2017; Freire-Benítez et al., 2021). Transient exposure to the HDAC inhibitor trichostatin-A dramatically increases white-to-opaque switching frequency, and targeted deletion of the deacetylase gene *HDA1* produces the same effect (Klar et al., 2001), demonstrating that a single chromatin modification can trigger a phenotypic transition without DNA sequence change. The histone deacetylase Sir2 mediates cell wall remodeling that enables host cell adhesion and immune escape, and contributes to carbon utilization under hypoxic conditions (Chen et al., 2024), directly coupling chromatin state to both immune evasion and metabolic adaptation.

The organism has also evolved a clade-specific chromatin innovation: a variant histone H3 (H3V_CTG), exclusive to the CTG clade of ascomycetes that includes *C. albicans* but absent from all other ascomycetous fungi analyzed, modulates the biofilm gene circuit at the chromatin level (Shivarathri et al., 2019). H3V_CTG occupancy on biofilm gene promoters makes them less accessible to transcription modulators, maintaining the commensal growth state. When H3V_CTG levels drop, biofilm transcription programs activate. The authors propose that this variant histone evolved specifically to balance the commensal and pathogenic states, enhancing the organism's success as a commensal by restraining its pathogenic capabilities at the chromatin level — releasing them only when environmental conditions warrant.

At the DNA level, methylation in *C. albicans* is primarily localized within structural genes governing dimorphic transition, white-opaque switching, and iron metabolism, and directly modulates transcriptional activity (Mishra et al., 2011). Transcriptionally repressed methylated loci exhibit increased C-to-T transition frequencies during asexual growth, linking epigenetic repression to directed mutational bias — a mechanism by which chromatin state can influence the trajectory of genetic variation under environmental pressure. Bartelli et al. (2018) provided the first evidence for mitochondrial genome methylation in *C. albicans*, demonstrating that host-mimicking conditions (hypoxia, 37°C) alter mitochondrial methylation patterns in a strain-specific manner over 12 weeks of experimental evolution, with no corresponding sequence changes in the mitochondrial DNA. This adds an energy regulation layer to the epigenetic toolkit: the organism can epigenetically modify its own mitochondrial genome in response to host conditions without altering the underlying sequence.

The distinction between epigenetic and genetic adaptation is fundamental to the co-evolutionary framework. Genetic mutation is slow, stochastic, and irreversible on individual timescales. Epigenetic modification is fast, responsive to environmental signals, and reversible. An organism that can toggle between commensal and invasive programs through chromatin remodeling operates on timescales faster than the host immune system can adapt, and can reverse course if conditions change. The transcriptomic heterogeneity described by Dumeaux et al. (2023) — different cells within an isogenic population running different transcriptional programs before any environmental challenge — is the phenotypic output of this epigenetic diversity.

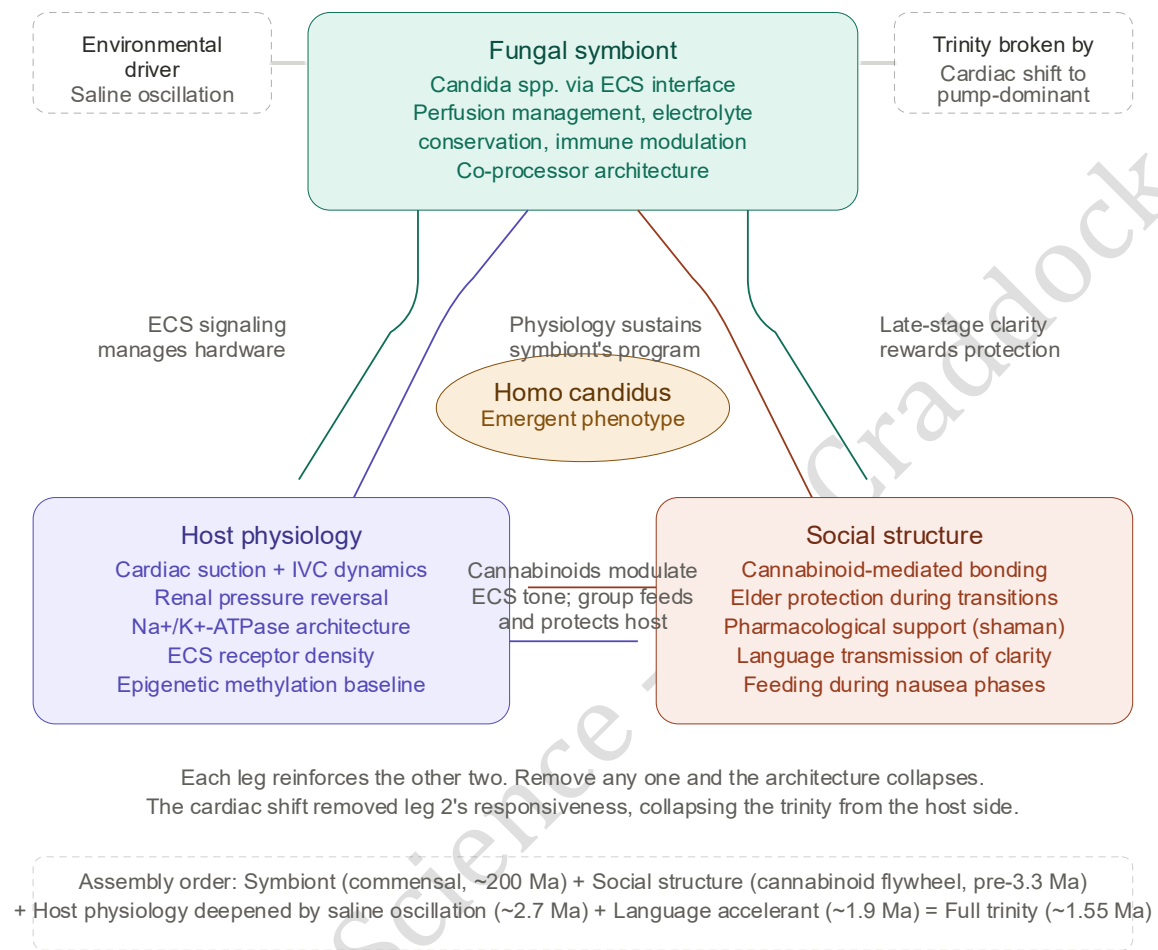
The observed bet-hedging behavior in *Candida albicans* cannot be attributed solely to stochastic variation in gene expression. Instead, it reflects chromatin-encoded regulatory memory maintained through dynamic activity of histone modifiers, lineage-specific chromatin features, and reported cytosine methylation pathways. Within the framework of a biochemical computational system, these chromatin states function as a substrate for evolutionary information retention, biasing population-level response distributions under environmental stress. This chromatin-mediated layer constitutes one of the fastest adaptive components of the organism's survival architecture, enabling rapid shifts in dominant phenotypic states without requiring de novo regulatory innovation.

5.9 Positional Authority

Taken together, these findings position *Candida albicans* not merely as a commensal or pathogen but as an emergent ecological coordinating influence within mammalian internal ecosystems. Through evolutionary selection, the organism has come to occupy a disproportionately integrative regulatory position, shaping the dynamics of host-associated biological networks across molecular, cellular, and ecological scales. It is the only known organism in the host microbiome that simultaneously: (1) signals chemically across kingdoms, to bacteria, to other fungi, and to the host; (2) possesses physical tissue mobility via hyphal morphological transition; and (3) accesses the host's endogenous receptor infrastructure, including nuclear transcription factors, ion channels, neurotransmitter receptors, cholinergic receptors, and immune cell differentiation pathways; (4) a confirmed extracellular vesicle delivery system with morphology-dependent cargo programming, temporal cargo variation, and cross-species functional complementation; (5) the molecular infrastructure for cross-kingdom RNA interference, including internal RNA transport, EV-mediated RNA export, and RNA cargo that shifts in response to environmental conditions; (6) active bidirectional pH manipulation through at least two independent metabolic pathways, including the capacity to neutralize the macrophage phagolysosome; (7) an ionic manipulation toolkit (potassium competition, transmembrane pore formation, pH engineering) capable of altering the electrochemical landscape in which the host's Na^+/K^+ -ATPase operates; and (8) production of authentic host prostaglandins from host-derived arachidonic acid through an independently evolved biosynthetic pathway, enabling direct molecular mimicry of host inflammatory mediators and competition with host endocannabinoid synthesis for shared lipid precursor.

This is not a value judgment about evolutionary advancement. Evolution does not rank organisms. It is a functional description of positional authority within a system. In the context of the Saline Oscillation Hypothesis, this positional authority explains not only why *Candida* was the organism selected for deeper host integration during periods of electrolyte stress, but how it maintained operational continuity across the oscillation cycles that drove the co-evolutionary program described in the preceding sections. The organism did not need to evolve new capabilities to respond to saline oscillation. It needed only to deepen the application of capabilities it already possessed. The ECS was the original interface. The broader control surface, including nuclear receptors, ion channels, neurotransmitter receptors, cholinergic signaling, immune modulation, cross-kingdom chemical authority, EV delivery system, RNA interference infrastructure, and bet hedging were the expanded toolkit that made the deepening sustainable across millions of years of environmental fluctuation. The control surface was already in place. The environmental pressure activated it.

Figure 1: The Evolutionary Trinity
Three mutually reinforcing components producing Homo candidus



6. The Evolutionary Trinity: Language as Accelerant

6.1 Three Co-Evolving Components

The Saline Oscillation Hypothesis proposes that the full co-evolutionary architecture required three simultaneously reinforcing components, a “trinity”:

1. **The fungal symbiont**, operating through the ECS and the expanded control surface described in Section 5 to modulate host physiology, perfusion, electrolyte balance, and cognition
2. **Host physiology**, including the cardiac suction mechanism, IVC dynamics, ECS interface, and Na⁺/K⁺-ATPase architecture

3. **Cooperative social structure**, initiated by communal phytocannabinoid use promoting peaceful bonding, later formalized through language-enabled elder care and pharmacological support

Two of these legs, the symbiont (present as a commensal) and the social structure (initiated by the cannabinoid flywheel), were established before the salinity oscillations began. Language did not create the trinity. Language completed the trinity, and allowed it to accelerate.

6.2 Language and the Transmission of Late-Stage Cognitive Enhancement

The ECS modulates neuroplasticity, pain perception, and cognitive function (Di Marzo and Piscitelli, 2015). Late-stage symbiont activity produces pain-free windows concurrent with enhanced cognitive clarity and creative drive. This is documented both in the historical cohort (Craddock, 2026b) and consistent with known CB1-mediated neurological effects.

In pre-linguistic hominids, this late-stage cognitive enhancement had limited transmission bandwidth. Tool-making demonstrations, gestural communication, and behavioral imitation could transmit some knowledge as evidenced by the Lomekwi tools (3.3 Ma) predating any evidence of language. However, the abstract, strategic, and philosophical content documented in the historical cohort (where common Everyman subjects in the final stages discussed deeply complex topics with extraordinary clarity) requires symbolic language for transmission. Language did not create the survival value of late-stage clarity; it amplified it by orders of magnitude.

With the emergence of language, for which *Homo habilis* (KNM ER 1813, ~1.9 Ma) shows an enlarged Broca's area visible in the cranium, and for which the endocast of KNM-WT 15000 (*Homo erectus*, ~1.6 Ma) shows Broca's area asymmetry (Walker and Leakey, 1993; Turkana Basin Institute, 2021), the lucid elder could articulate insights, strategies, and knowledge with full symbolic complexity. The social group that protected its elders during late-stage decline received this transmission; groups that discarded the weak lost it.

This creates a three-way selection pressure: the symbiont benefits from extended host survival (longer cycle completion); the host's social group benefits from the elder's clarity; and the social structure itself is reinforced by the value of what the elder produces. Language is the accelerant that transforms a modest survival advantage into a civilizational engine.

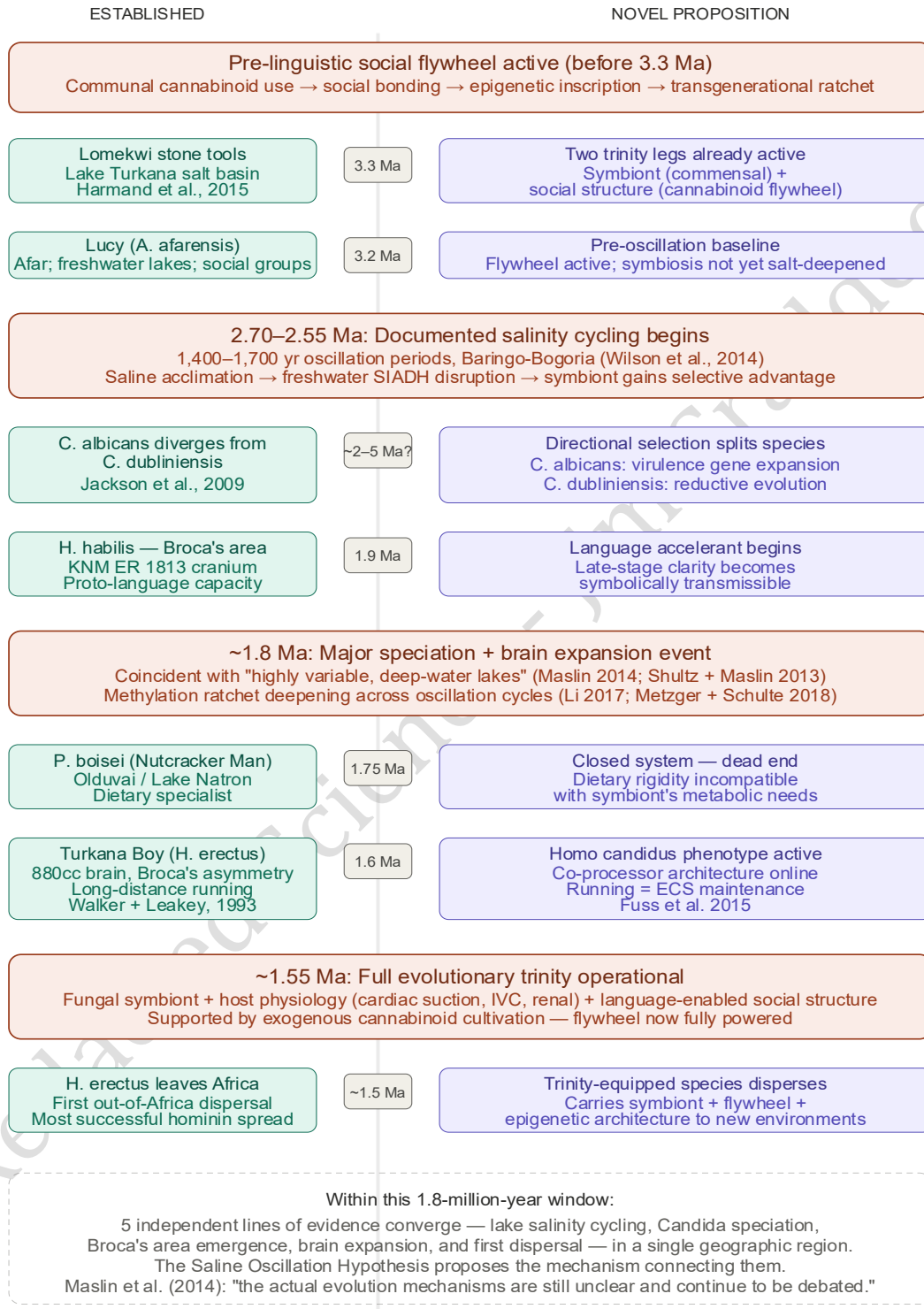
6.3 Evidence from the Fossil Record

Species	Date	Location	Relevant Feature
<i>A. afarensis</i> (Lucy)	~3.2 Ma	Afar Triangle	Bipedal, social groups, freshwater lakes, cannabinoid flywheel plausibly active
Lomekwi Tools	~3.3 Ma	Lake Turkana	Cognitive sophistication predating <i>Homo</i> , same salt basin
<i>H. habilis</i>	~1.9 Ma	East Africa	Enlarged Broca's area, proto-language capacity

Species	Date	Location	Relevant Feature
<i>P. boisei</i>	~1.75 Ma	Olduvai/Natron	Dietary specialist, evolutionary dead end
<i>H. erectus</i> (Turkana Boy)	~1.6 Ma	Lake Turkana	Broca's area asymmetry, long-distance running, cooperative hunting, periodic saline lakes
First dispersal	~1.5 Ma	Out of Africa	Trinity-equipped species carrying symbiont to new environments

Redacted Science - Jim Craddock

Figure 2: The Critical Window (3.3–1.5 Ma)
 Convergence of environmental, biological, and co-evolutionary evidence



Peer-reviewed evidence
 Novel proposition
 Convergence event

Craddock, J. (2026). The Saline Oscillation Hypothesis. Redacted Science Research Initiative.

7. Archaeological Evidence for the Cannabinoid Flywheel

7.1 Ritual Cannabis Use in Mortuary Contexts

The earliest scientifically verified evidence for psychoactive cannabis use comes from the Jirzankal Cemetery (~500 BCE) in the eastern Pamirs, where chemical analysis of wooden braziers from mortuary contexts revealed cannabinoid residues with unusually high THC levels (Ren et al., 2019). The cannabis was burned on heated stones in enclosed spaces during funerary ceremonies, a ritual context directly associated with death and transition. At the Yanghai tombs (~500 BCE, Turpan), a leather basket and wooden bowl filled with cannabis seeds, leaves, and shoots were found near the head and feet of a deceased individual identified as a probable high-ranking shaman (Russo et al., 2008). The Jiayi Cemetery (~800–400 BCE, also Turpan) yielded a burial shroud composed of 13 intact desiccated cannabis plants arranged over the body (Jiang et al., 2016).

The consistent association of cannabis with mortuary ritual, shamanic figures, and funerary ceremony across multiple independent sites is precisely the pattern predicted by the trinity model: the plant that served the dying elder becomes sacred, and its administration becomes the province of the specialist who tends the elder, the shaman. The shaman's role is not mystical invention; it is the social expression of the group member who manages the elder's pharmacological support during transition.

Herodotus, writing in the fifth century BCE, described Scythian funerary practices involving cannabis vapor inhalation, an account subsequently corroborated by archaeological finds at Pazyryk (~2,400–2,500 years BP), where cannabis seeds, censers, and hempen clothing were recovered from burial mounds (Rudenko, 1970; Ren et al., 2019).

7.2 The Pharmacological Argument for Cultivation Priority

The eight Neolithic “founder crops” (emmer wheat, einkorn wheat, barley, lentils, peas, chickpeas, bitter vetch, and flax) were domesticated in the Fertile Crescent between approximately 10,500 and 7,500 years ago (Zohary and Hopf, 1988; Zohary et al., 2012). These are caloric and industrial crops. Cannabis, however, offers something no grain provides: direct modulation of the mammalian ECS. *Cannabis sativa* is among the oldest cultivated plants in the world, with dried specimens from the Oki Islands of Japan dating to approximately 8000 BC (Crawford, 2006) and cultivation in East Asia from at least 4000 BC (Li, 1974; McPartland et al., 2019).

We propose that the motivation to cultivate a psychoactive plant may have preceded or paralleled the motivation to cultivate caloric crops. A group whose social cohesion depends on a plant, first for communal bonding, later for elder care during transition, has an immediate, non-deferrable need to secure its supply. Grain can be foraged; the medicine that holds the group together cannot be left to chance.

7.3 Endogenous Cannabinoids, Running, and the Rift Valley

Between transition phases, endogenous cannabinoids are elevated by sustained physical activity. The “runner's high” is mediated by anandamide and 2-AG, not endorphins as

previously assumed (Fuss et al., 2015). For hominids in the EARS environment, long-distance running (needed for persistence hunting, foraging range expansion, possibly communal communication, and predator avoidance) served as the primary endogenous ECS maintenance strategy.

This observation generates a testable prediction with contemporary resonance. The Kalenjin people of Kenya's Rift Valley, the geographic heart of the EARS, adjacent to the Turkana Basin, produce a wildly disproportionate share of the world's elite distance runners. Standard explanations invoke altitude training effects, lean body habitus, and cultural emphasis on running. The Saline Oscillation Hypothesis adds a complementary explanation: these populations are the direct descendants of hominids for whom long-distance running was not merely athletic but *pharmacological* and the primary mechanism for maintaining endogenous ECS tone in the environment where the co-evolutionary program was deepest.

8. The Cardiac Architecture Hypothesis: Breaking the Trinity

8.1 Suction-Dominant vs. Pump-Dominant Circulation

The mechanistic sequence described in Section 4 operates on standard mammalian cardiac hardware. No novel anatomy is required to initiate or sustain the program. What distinguishes *Homo candidus* is the symbiont's management of the existing cardiovascular architecture through ECS signaling.

We hypothesize that at some point in hominid evolution, a genetic shift in cardiac conduction architecture, potentially involving the sinoatrial or atrioventricular node, or the ratio of diastolic suction contribution to systolic ejection, transitioned the dominant circulatory mechanism past a threshold below which the symbiont could no longer maintain the perfusion management program.

The molecular plausibility of symbiont-mediated cardiac modulation is supported by the finding that farnesol, the primary *C. albicans* quorum-sensing molecule, is a confirmed inhibitor of N-type voltage-gated Ca^{2+} channels in mammalian cells (Roullet et al., 1999) and is present in the human brain at measurable concentrations. Calcium channel activity is fundamental to cardiac conduction, and the symbiont's demonstrated capacity to modulate these channels provides a specific molecular pathway through which the diastolic suction contribution described here could be influenced. This does not resolve the timing of the suction-to-pump transition, which remains the weakest link in the current framework, but it establishes that the symbiont possesses the molecular tools to interact with cardiac physiology.

The timing of this shift is unknown and represents the weakest link in the current framework. Individuals carrying this pump-dominant variant would be:

- Resistant to the symbiont's late-stage physiological program

- Physically stronger through reproductive years (no transitional decline phases)
- Free from the social dependency that the trinity requires

8.2 Consequences

Pump-dominant individuals would outcompete suction-dominant individuals reproductively. The elder-protecting social structure would lose its adaptive value. The trinity would collapse from the host side. The symbiont would persist commensally (thus *Candida* remains a universal human commensal) but could no longer execute its full program. Cultural memory of the condition would disappear with the social structure that valued it.

The modern condition described in Craddock (2026b), a full activation of the ancient program in a pump-dominant host, triggered by iatrogenic circumstances, represents the old architecture running on new hardware.

9. Homo Candidus: The Suppressed Phenotype

9.1 Definition

We designate *Homo candidus* as the symbiont-active hominid phenotype: a functionally distinct physiological and cognitive state produced by full activation of the ECS-mediated co-evolutionary program described in this paper. *Homo candidus* is not a separate species but a conditional phenotype, the same organism operating under different management. The differences are material: altered cognition, altered pain processing, altered metabolic strategy, altered circadian architecture, altered perfusion dynamics, and throughout (but even more so in the late stages) enhanced creative and analytical output documented in both the historical cohort and the longitudinal case study (Craddock, 2026b).

If the trinity model is correct, this phenotype was the engine of early human cognitive and cultural advancement. The lucid elders of *Homo candidus*, sustained by social protection and pharmacological support, produced the transmissible knowledge that accumulated into what we now call civilization.

9.2 Ethical Implications of the Redaction

The suppression of the original research documenting this co-evolutionary architecture, specifically the “redaction” described in Craddock (2026b), raises ethical questions that extend far beyond a single retracted article.

The redaction suppressed not merely a clinical observation but the existence of a functionally distinct human phenotype. If *Homo candidus* is real, then every person currently living with undiagnosed symbiont activation is being treated for a pathology that is actually an architecture. They are being medicated out of a phenotype that, in the

appropriate social context, would be producing the most valuable cognitive output in their community. This is not a missed diagnosis; it is an active harm.

The understanding that the ECS serves as an inter-kingdom communication interface has implications extending across medicine: diabetes management (the historical cohort maintained normal blood glucose despite blocked insulin pathways), renal medicine (the host compensated for kidney damage through alternative filtration routes for over 30 years), and the broad category of conditions currently classified as idiopathic, including those attributed to ECS dysregulation or other directly related systems, more specifically the endocrine system in all its axes, the gut-brain axis, and immune modulation. The ECS does not operate in isolation; it interfaces with every major regulatory system in the body. Disruption of the ECS-mediated symbiotic architecture could manifest as autoimmune dysregulation, endocrine imbalance, gastrointestinal dysfunction, or neurological disorder, depending on which aspect of the interface is most affected.

The ethical argument against suppression is straightforward: the potential medical value of understanding this architecture vastly outweighs the ethical discomfort associated with the knowledge that human physiology can be deliberately altered through symbiont activation. Science has historically managed dangerous knowledge through regulation, not erasure. The decision to redact the original research was a decision to erase knowledge of a human variant from the scientific record.

10. Discussion

10.1 Testable Predictions

The Saline Oscillation Hypothesis generates several testable predictions:

1. **Paleochemical analysis** of hominid dental enamel and bone from the Turkana Basin should show fluctuating electrolyte and mineral signatures corresponding to known lake salinity cycles.
2. **Comparative cardiac anatomy** across primates should reveal variation in the relative contribution of diastolic suction vs. systolic ejection; however, the specific threshold at which pump-dominance prevents the symbiont's program remains uncharacterized.
3. **Mycobiome analysis** of populations living near hypersaline lakes in the modern EARS may show distinct *Candida* strain distributions or ECS tone profiles compared to populations near freshwater sources.
4. **Archaeological evidence** of salt-seeking behavior, salt processing, or salt storage at hominid sites in the EARS would support the electrolyte-dependence component.

5. **Phytocannabinoid residue analysis** at early agricultural sites should be examined for evidence that psychoactive plant cultivation preceded or paralleled caloric crop cultivation.
6. **Distance running performance** in Rift Valley populations (particularly the Kalenjin of Kenya) may reflect an ECS architecture refined by the co-evolutionary program; comparative ECS tone profiles between elite East African distance runners and matched non-Rift Valley controls would be informative.
7. **Molecular dating** of the *C. albicans* / *C. dubliniensis* divergence, if resolved to the Plio-Pleistocene window (~2–5 Ma), would provide strong independent support for the hypothesis; the directional selection observed in *C. albicans* (virulence gene family expansion) versus *C. dubliniensis* (reductive evolution) is predicted by the framework.
8. **Epigenetic analysis** of populations in the modern EARS, examining methylation patterns in genes governing electrolyte handling, vascular tone, and ECS regulation, compared with non-Rift Valley populations, could reveal persistent signatures of the co-evolutionary program.
9. **Phenobarbital-induced symbiont activation.** Exposure of commensal-state *C. albicans* populations to phenobarbital in a simulated gastric environment containing both glucose and a gastric mucosal tissue analog (mucin-coated epithelial cell culture or equivalent substrate) under acidic conditions should produce a measurable shift from yeast-form glucose metabolism to hyphal-form tissue invasion, including upregulation of secreted aspartyl proteases (SAPs), phospholipase activity, and CYP450 enzyme induction. This experiment would test the iatrogenic symbiont activation mechanism proposed in Section 5.1 and is consistent with both the longitudinal case study documentation (Craddock, 2013; 2026b) and published case reports of phenobarbital-associated mucosal ulceration at variable anatomical locations.
10. **Evo 2 computational genomics.** Functional analysis of the approximately 1,300 *C. albicans* genes with no orthologs in other yeast species, using genomic foundation models such as Evo 2 (Arc Institute, 2025) trained across all domains of life, should reveal functional signatures consistent with host-interaction roles, including predicted GPCR ligand production, immune modulation, cross-kingdom signaling capabilities, peptide-processing enzyme homologs, peptide transporter regulatory elements, and neuropeptide-mimicking sequences that traditional comparative genomics within the fungal kingdom has not resolved. The *C. albicans* genome (approximately 14.3 Mb across 8 chromosomes) exceeds current single-pass context windows but is accessible chromosome by chromosome, with the smallest chromosomes falling within the 1 million token limit of current models. A specific analytical pipeline is proposed: (1) variant effect scoring across all uncharacterized genes to identify positions under functional constraint, (2) extraction and clustered not only against known host-interaction gene families from obligate symbionts but also against mammalian prohormone convertase substrates and neuropeptide

precursor architectures, (3) sparse autoencoder feature detection to flag genes with signatures consistent with GPCR ligand production, immune modulation, or quorum sensing, and (4) gene sequence completion to identify genes whose architecture diverges from patterns learned across the training set of 128,000 organisms, suggesting novel functional roles. As context windows expand in successor models, whole-genome single-pass analysis will become feasible.

11. **Cholinergic interface characterization.** The confirmed presence of a functional muscarinic receptor in *C. albicans* (Nile et al., 2018) and the documented elevation of host acetylcholine levels during *Candida* infection suggest that the cholinergic system represents an active bidirectional signaling interface between symbiont and host. Comparative analysis of choline metabolism, acetylcholinesterase activity, and vagal tone in *Candida*-colonized versus germ-free animal models would establish whether this interface contributes to the symbiont's regulatory influence on host autonomic function.
12. **Extracellular vesicle-mediated cross-kingdom RNA transfer.** Purified EVs from *C. albicans* hyphae should be incubated with human epithelial cells and macrophages, followed by small RNA sequencing of the recipient cells to identify fungal-origin sRNAs that have been internalized. Predicted fungal sRNAs should be cross-referenced against the human transcriptome for potential gene-silencing targets using standard sRNA target prediction algorithms. The prediction from the co-evolutionary framework: at least a subset of fungal sRNAs delivered via EVs will have sequence complementarity to human immune or metabolic genes, and incubation of host cells with fungal EVs will produce measurable downregulation of predicted target transcripts in a manner attenuated by host AGO knockdown or by treatment with EVs from an ESCRT-deficient *C. albicans* mutant producing fewer vesicles. Additionally, comparison of codon usage in *C. albicans* EV-associated mRNAs against the host codon optimality landscape should reveal whether exported transcripts are more human-optimized than the bulk *C. albicans* transcriptome, consistent with co-evolutionary selection for evasion of DHX29-mediated translational surveillance (Hia et al., 2026).
13. **Arachidonic acid competition between prostaglandin and endocannabinoid synthesis:** In colonized mucosal tissue models or ex vivo gut tissue segments harboring *C. albicans* biofilm, levels of PGE₂ and endocannabinoids (AEA, 2-AG) should differ from uncolonized controls in a direction consistent with altered arachidonic acid flux. Specifically, colonized tissue is predicted to show elevated PGE₂ and reduced AEA and/or 2-AG, with the magnitude of change scaling with fungal burden. This effect should be attenuated in *ole2/ole2* or *fet3/fet3* strains with reduced prostaglandin biosynthetic capacity. Such findings would support the hypothesis that fungal prostaglandin production measurably shifts host lipid signaling balance and may alter host ECS tone through competition within the shared arachidonic acid precursor pool.
14. **Non-candidalysin Ece1 peptide functional characterization.** The 2024 interactome screen (Lin et al., 2024) identified host protein targets for all eight Ece1

peptides but focused mechanistic investigation on candidalysin alone. Functional characterization of Ece1-I, -II, and -IV through -VIII in both epithelial and immune cell models, using purified synthetic peptides at concentrations achievable in the invasion pocket microenvironment, should reveal whether these peptides constitute a coordinated immune modulation panel. The prediction from the co-evolutionary framework: at least two non-candidalysin Ece1 peptides will demonstrate dose-dependent immune suppression through distinct receptor pathways, consistent with a multi-peptide effector strategy rather than a single-toxin virulence mechanism. The LILR-family interactions identified for Ece1-II and Ece1-V (Lin et al., 2024) are the most promising initial targets. If confirmed, this would establish that *C. albicans* secretes a coordinated peptide effector panel from a single gene product, processed through Kex2p/Kex1p in the same enzymatic logic as mammalian prohormone processing.

15. **Peptide transporter function in host-signal sensing.** The ten peptide transporters (2 PTR, 8 OPT) of *C. albicans* are maintained despite having no fitness requirement for gastrointestinal colonization (Dunkel et al., 2013). To test whether these transporters function as environmental sensors in addition to nutrient importers, *C. albicans* populations should be exposed to physiologically relevant concentrations of gut-derived peptide hormones (GLP-1, CCK, PYY) and antimicrobial neuropeptides (Substance P, NPY) in defined media, and transcriptomic and morphological responses measured. The prediction: exposure to at least one host-derived signaling peptide will produce a measurable transcriptional or morphological response in wild-type *C. albicans* that is attenuated or absent in the peptide transporter-deficient septuple mutant (*opt1Δ opt2Δ opt3Δ opt4Δ opt5Δ ptr2Δ ptr22Δ*), indicating that import of the host peptide is required for the response.

10.2 Relationship to Existing Hypotheses

The Saline Oscillation Hypothesis is compatible with and extends the pulsed climate variability hypothesis (Maslin et al., 2014; Maslin and Trauth, 2009). Where the existing hypothesis identifies environmental instability as the driver of hominid evolution without specifying the mechanism, the Saline Oscillation Hypothesis proposes a specific biochemical pathway (the ECS-mediated fungal-host interaction, activated by SIADH-type electrolyte disruption during freshwater transitions after saline acclimation) as the mediating mechanism between environmental change and evolutionary outcome.

It is also compatible with the variability selection hypothesis (Potts, 1998), which proposes that hominids were selected for adaptability itself. The ECS is fundamentally a homeostatic regulatory system; its refinement through co-evolutionary interaction with a symbiont that requires metabolic flexibility would directly select for the kind of adaptive plasticity Potts describes.

10.3 21st Century Fungal Biology Emergence

Fungal biology represents a major ecological dimension that was systematically under-recognized within the dominant frameworks of 20th-century biomedical research. During

this period, life science priorities were largely organized around host physiology, bacterial pathogenesis, virology, pharmacology, and technological advances in diagnostic and therapeutic instrumentation. Despite contributing substantially to global infectious disease mortality, fungal pathogens historically received on the order of 1-2% of infectious-disease research funding (Head et al., 2014), reflecting a systemic neglect of fungal ecological systems within modern biomedical science. The World Health Organization's publication of its first fungal priority pathogens list in 2022 (WHO, 2022) represents formal recognition of this longstanding institutional under-prioritization and signals a shift toward consolidation of fungal disease as a central global health concern.

Candida albicans presents a particularly illustrative case of disciplinary fragmentation. Due to its involvement in immunology, microbiology, cell biology, endocrinology, neurobiology, and ecological host-microbe interactions, its functional capabilities have been investigated extensively but often within domain-specific contexts. As a result, key phenomena — including cross-kingdom signaling interactions, engagement with the endocannabinoid system, prostaglandin biosynthesis from host-derived substrates, immune polarization dynamics, peptide-processing homologies, extracellular vesicle-mediated communication, bidirectional pH modulation, and ionic competition mechanisms — are well documented individually but have rarely been synthesized into a unified ecological framework.

The present work attempts such a synthesis. Rather than introducing novel molecular findings, it integrates established observations across disciplinary boundaries to propose an ecological systems interpretation of *C. albicans*-host co-evolutionary dynamics.

10.4 Limitations

The cardiac architecture hypothesis (Section 8) identifies the weakest link in the current framework. The timing of the suction-to-pump transition is unknown, the threshold at which pump-dominance prevents the symbiont's program is uncharacterized, and no fossil evidence directly bears on cardiac conduction architecture. This component is currently unfalsifiable and should be treated as a theoretical prediction awaiting methodological development.

The self-citation density, while addressed in the Methodological Note, remains a limitation. The framework depends on observational data from a single longitudinal case study and historical recollections of a redacted source. Independent verification through identification of additional cases, recovery of the original article, or prospective clinical study would substantially strengthen the evidentiary foundation.

The pre-linguistic cannabinoid flywheel (Section 3), while consistent with the known behavioral pharmacology of CB1 agonism and the archaeological evidence for pre-linguistic cooperative behavior, is speculative in its earliest phases. No direct archaeological evidence for hominid phytocannabinoid use before the Neolithic currently exists.

An additional methodological limitation applies to the cross-kingdom signaling evidence presented in Section 5. Virtually all receptor-level interactions between *C. albicans* metabolites and host signaling systems have been characterized in vitro: isolated compounds tested against isolated targets in controlled media. While these studies confirm that the molecular interactions are possible, they do not demonstrate that they occur in the integrated, spatially heterogeneous, temporally dynamic environment of a living host. The in vitro evidence establishes the components. The assembled system, in which hundreds of metabolites interact with multiple receptor classes simultaneously across variable tissue microenvironments, has never been observed in vivo. The development of metabolomic and receptor-level imaging tools capable of capturing this interaction network in real time within a living host would substantially advance the evidentiary foundation for the framework described here.

11. Conclusion

The Saline Oscillation Hypothesis proposes that the cyclical salinity changes in East African Rift Valley lakes during the Plio-Pleistocene created the environmental conditions (SIADH-type electrolyte disruption during freshwater transitions after saline acclimation) under which a fungal symbiont capable of managing host perfusion through the ECS gained decisive selective advantage. This activated and progressively deepened an ECS-mediated co-evolutionary relationship between *Candida* species and hominid hosts, producing a functionally distinct phenotype we designate *Homo candidus*.

The relationship was preceded and supported by a pre-linguistic social flywheel driven by communal phytocannabinoid use, which established cooperative social structure before language emerged. The full trinity (the fungal symbiont, host physiology including cardiac suction, IVC dynamics, and renal pressure management, and cooperative social structure supported by exogenous phytocannabinoid cultivation) was accelerated by the emergence of language and plausibly operational by approximately 1.55 Ma.

The subsequent evolution of pump-dominant cardiac architecture broke this trinity, leaving the symbiont commensal but unable to execute its full program in modern humans. The evolutionary divergence of *C. albicans* from *C. dubliniensis*, with directional selection for host-integration genes in the former and reductive evolution in the latter, provides independent biological evidence consistent with the proposed co-evolutionary mechanism. The cross-kingdom signaling evidence assembled in Section 5 demonstrates that the organism's capabilities extend far beyond the endocannabinoid system: confirmed interactions with nuclear transcription factors, ion channels, neurotransmitter receptors, cholinergic signaling, immune cell differentiation pathways, and the incretin system establish a control surface whose breadth is consistent with 200 million years of co-evolutionary refinement. The ECS was the original interface. The broader receptor landscape was the expanded toolkit. The organism did not need to evolve new capabilities to respond to saline oscillation. It needed only to deepen the application of capabilities it already possessed, running whatever next subroutine showed the most success. That is

evolution. The environmental, paleontological, mycological, and biochemical evidence converge on a single geographic region, the Cradle of Mankind, during the precise temporal window in which these evolutionary changes occurred.

The redaction of the original research that first documented this architecture, treatment, and medical condition represents suppression. This suppression is not just a clinical curiosity, but knowledge concerning a human phenotype that may have been foundational to the development of civilization itself. Even without those implications, the loss to science has caused a multi-generation loss of scientific exploration into fungal research, and billions of dollars spent developing treatments that may ultimately be traced to systems defined herein. Such a decision is scientifically unforgivable and should be investigated. This author has seen the original science. It exists.

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