From Indoles to Tryptophan

Reclassification of *Physarum polycephalum* Deepens the Signaling Hypothesis by 1.5 Billion Years

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Abstract

A companion paper proposed that psilocybin's primary ancestral function is intercellular signaling within mycelial networks, built on the conserved tryptophan-derived indole scaffold. This paper extends that conjecture downward in evolutionary time. It begins by correcting a taxonomic point in the earlier work—*Physarum polycephalum*, long grouped with fungi, is now resolved within Amoebozoa, the sister supergroup to the Opisthokonta that contains both fungi and animals—and then argues that the correction, far from weakening the signaling conjecture, deepens it. If an amoebozoan separated from fungi by roughly 1.5 billion years of independent evolution coordinates its behavior through chemical signaling built on the same amino-acid precursor, then the signaling architecture predates the fungal lineage entirely. The precursor is tryptophan, and the indole scaffold derived from it is reused across kingdoms—auxin in plants, serotonin and melatonin in animals, the psilocybin family in fungi—as the substrate of distributed biological coordination. This paper is a worked instance of a principle the corpus relies on throughout: that conserved molecules are characteristically multifunctional, elaborated by reuse rather than reinvented, so that cross-kingdom receptor compatibility is inheritance rather than coincidence. The claims are advanced as conjecture with named tests.

A Note on Status and Relationship to the Corpus

This was originally written as an addendum to the dual-drift / mycelial-signaling paper (Paper One of this corpus). It is presented here as a standalone paper because its argument—that tryptophan-based signaling is an inheritance older than fungi, animals, or plants as distinct lineages—stands on its own and bears on the whole corpus, not only on the parent paper. It should be read alongside Paper One (which states the signaling conjecture and the multifunctionality principle) and the companion chemical-ecology paper (which argues that the primary function is unlikely to be defence). As throughout the corpus, the central claims are conjecture with explicit tests, in a field whose thinness is a direct legacy of prohibition rather than of the questions being uninteresting.

1 A Taxonomic Correction, and Why It Deepens Rather Than Weakens the Conjecture

The parent paper cited *Physarum polycephalum* as an example of distributed intelligence and complex coordination in an organism then loosely grouped with fungi. That grouping rested on a longstanding convention placing plasmodial slime molds within Mycetozoa—a classification that persisted through much of the twentieth century and into standard references well into the 2000s.

Modern phylogenomics resolves *P. polycephalum* within **Amoebozoa**, the sister supergroup to **Opisthokonta** (which contains both fungi and animals). The divergence between Amoebozoa and Opisthokonta is estimated at roughly 1.4–1.6 billion years ago (Cavalier-Smith, 2003; Adl et al., 2012; Schaap et al., 2016). This is not a reshuffling within a phylum; it is a *supergroup-level* separation, comparable in phylogenetic distance to the animal–plant divergence rather than to the distance between, say, arachnids and insects within a single phylum. The record is corrected accordingly.

Two points follow, and both strengthen rather than weaken the signaling conjecture.

First, the conjecture never relied on *Physarum*. It was one illustrative example among several, chosen because its behavioral repertoire—maze-solving, network optimization, anticipatory behavior, memory—so conspicuously implied sophisticated internal signaling. The load-bearing elements are independent of it: fungi produce a suite of structurally related indolamines; indolamines function as signaling molecules in every kingdom where they appear; fungi exhibit coordinated behaviors that require chemical communication; and fungi share closer ancestry with animals than with any other major lineage, which accounts for cross-kingdom receptor compatibility. Remove *Physarum* and the argument stands intact.

Second—and this is the deepening—the very fact that makes the correction necessary is itself evidence. *Physarum* sits a supergroup away from fungi, yet it too coordinates its behavior through chemical signaling, and it does so using molecular architecture built on the same precursor. An organism that distant from fungi running the same kind of signaling chemistry does not undercut the conjecture that fungi signal this way; it implies the signaling is older than the fungal lineage altogether. The reclassification moves *Physarum* from "a fungus that signals" to "a distant relative that signals the same way"—which is the stronger evidence, because convergence at that phylogenetic distance is far less likely than inheritance.

Even setting *Physarum* aside entirely, true fungi—the mycelia of basidiomycetes, ascomycetes, and their kin—display behaviors impossible to explain without complex chemical signaling: allocating resources across meters of substrate, rerouting around damage, exchanging nutrients with plant partners in balance-sensitive mycorrhizal trade, distinguishing self from non-self, and modulating growth and reproduction in response to environmental gradients. These are not passive processes; they require functional inner distinctions—here and there, self and other, favorable and toxic—and a system that navigates gradients and seeks homeostasis is a system that processes information. Information processing requires signaling. The question was never whether fungi signal. It is which molecules carry the signal.

2 The Multifunctionality Principle, Demonstrated in Deep Time

This paper is, among other things, the corpus's clearest empirical illustration of a principle stated in Paper One and relied on throughout: *conserved biological molecules are characteristically multifunctional, elaborated by reuse rather than reinvented.* Evolution does not mint a new molecule for each

new task; it conserves a working scaffold and recruits it again in new contexts. Multifunctionality and cross-lineage reuse are the signature of construction-by-conservation, and they are the rule, not the exception.

Tryptophan and its indole derivatives are the textbook case, and the rest of this paper is essentially a demonstration of the principle in deep time. One precursor, conserved since before the major eukaryotic supergroups diverged, is elaborated independently by each lineage into its own signaling system—and the receptors that recognize these molecules are conserved alongside them, which is why a molecule built for one lineage's signaling can be recognized by another's. Cross-kingdom receptor compatibility, on this view, is not coincidence and not a special relationship between any two kingdoms; it is the expected consequence of a reused scaffold and its co-conserved recognition machinery. Read this way, the deep-time evidence assembled below is not merely about psilocybin's ancestry—it is the ground on which the corpus's reuse-and-multifunctionality principle stands.

3 Tryptophan as Ancestral Signaling Substrate

The reclassification of *Physarum* reveals that the story begins earlier and deeper than indolamines. The parent paper proposed psilocybin as a fungal signaling molecule structurally homologous to serotonin. That proposal stands—but if an amoebozoan separated from fungi by 1.5 billion years also signals chemically, using architecture built on the same precursor, then the mechanism predates fungi entirely. The precursor is tryptophan.

3.1 Tryptophan's Central Role

Tryptophan, one of the twenty standard amino acids, is the biosynthetic precursor to a remarkable range of signaling molecules across all kingdoms. The pathway is conserved: tryptophan is synthesized via the shikimate pathway in bacteria, plants, and fungi, and is dietary-essential in animals. From this single starting point, evolution has produced, in three lineages:

- **Fungi:** tryptophan → tryptamine → 4-hydroxytryptamine → psilocybin (and baeocystin, norbaeocystin, norpsilocin), via the four-enzyme cluster characterized by Fricke et al. (2017).
- **Animals:** tryptophan → 5-hydroxytryptophan → serotonin → melatonin—serotonin modulating mood, cognition, appetite, sleep, and thermoregulation; melatonin regulating circadian rhythm.
- **Plants:** tryptophan → indole-3-acetic acid (auxin), the primary growth hormone governing phototropism, gravitropism, root development, and differentiation.

Three kingdoms, one precursor, three signaling systems—all built on the indole-ring scaffold inherited from tryptophan. This is the reuse principle written across the tree of life.

There is a striking confirmation of this deep-ancestry reading in living mammalian neural tissue, developed in the companion morphogenetic paper and noted here because it is precisely what the present thesis predicts. The dendritic-growth response that serotonergic indoles drive in cortical neurons is not specific to any one molecule: the simple tryptamine N,N-dimethyltryptamine, the fungal psilocybin family, and the structurally elaborate ergot-derived ergoline LSD all promote the same neuritogenesis and spine formation, through the conserved 5-HT2A receptor, abolished in each case by the same receptor antagonist (Ly et al., 2018). If the growth instruction were carried by the specific shape of one molecule, this class-wide convergence would be a coincidence demanding separate explanation for each compound. On the deep-ancestry reading it is not a coincidence at all:

what the fluent tissue reads is the conserved tryptophan-derived *root*, and each of these molecules is a dialect of it, so any member the tissue can read is executed as growth. The neural growth response is therefore the 1.5-billion-year-old inheritance made visible—the ancestral root, executed by tissue that still speaks it, regardless of which descendant dialect arrives.

3.2 Physarum and Tryptophan

Physarum engages tryptophan directly: it exhibits negative chemotaxis toward L-tryptophan, detecting and moving away from its gradients (Kincaid & Mansour, 1978)—active gradient detection and directional response, not passive diffusion. Its genome encodes the complete shikimate and aromatic-amino-acid pathways (Schaap et al., 2016), including the AROM pentafunctional polypeptide—the same gene-fusion architecture found in fungi, alveolates, and oomycetes, plausibly the ancestral state of that protein's domain organization. *Physarum* does not merely detect tryptophan; it synthesizes it, using the same enzymatic architecture as fungi.

3.3 The Unidentified Signaling Molecule

Alim et al. (2017) showed that *Physarum* coordinates body-wide behavior through a signaling molecule released on nutrient stimulus—advected by cytoplasmic flows while increasing contraction amplitude, generating a feedback loop that propagates information through the organism. The chemical identity of this molecule remains unknown, and that open question sits directly in the domain of the present conjecture. Given that *Physarum* synthesizes tryptophan via conserved pathways; that tryptophan-derived molecules are signaling molecules in every characterized lineage; that *Physarum* has an extensive GPCR repertoire (146 identified, including rhodopsin-like neuropeptide-receptor relatives; Schaap et al., 2016); and that it responds to mammalian neurotransmitters despite lacking a nervous system (Chet, Naveh, & Henis, 1977)—the most parsimonious conjecture is that *Physarum*'s unidentified signaling molecule is tryptophan-derived. This is a testable prediction, and a clean one: identify the molecule.

3.4 Neurotransmitter Responsiveness Without Neurons

Chet, Naveh, and Henis (1977) showed that *Physarum* responds to mammalian neurotransmitters despite having no nervous system: epinephrine reduced movement rate and shortened streaming cycles; amphetamine, cannabinol, and heroin each diminished movement; sodium barbital misdirected chemotactic response. More recently, propofol—the general anesthetic that blocks learning and memory in mammals—was shown to block learning in *Physarum* (Kippenberger et al., 2023): the organism that solves mazes and exhibits habituation is impaired by the same agent that impairs mammalian cognition.

These are not artifacts of receptor promiscuity but signatures of deeply conserved molecular-recognition architecture. The receptors and the molecules they bind were in place before Amoebozoa and Opisthokonta diverged; both lineages inherited them and elaborated them into lineage-specific systems, but the foundation—tryptophan-based molecular recognition—was already there. This is some of the strongest evidence in the corpus for inheritance over coincidence, and it is worth stating at full strength: a billion-and-a-half years of independent evolution, and the recognition machinery still answers to the same keys.

4 A Revised Signaling Hierarchy

The parent paper's "skeleton-key" argument—that psilocybin fits mammalian serotonin receptors through structural homology—stands, but the *Physarum* evidence shows the key has an older provenance than first appreciated. The revised hierarchy has three chapters:

Chapter One: Tryptophan. Selected as a signaling precursor before the Amoebozoa–Opisthokonta divergence (~1.4–1.6 Gya). Shikimate pathway and AROM architecture already in place; molecular recognition of tryptophan and its derivatives already functional. The foundation.

Chapter Two: Indolamine diversification. After that split, and after the later fungi–animal divergence (~0.7–1 Gya), each lineage elaborated tryptophan into its own signals: psilocybin and relatives in fungi, serotonin and melatonin in animals, auxin in plants. Same precursor, different elaborations, same functional role—chemical coordination of distributed systems.

Chapter Three: Cross-kingdom receptor compatibility. Psilocybin's affinity for mammalian 5-HT2A is not accident, curiosity, or special relationship; it is legacy inheritance. The recognition architecture allowing a fungal tryptophan derivative to bind an animal tryptophan-derivative receptor was established before either kingdom existed. The lock and the key were cut from one template and carried forward, independently, for over a billion years.

5 Memory Implies Signaling

Physarum displays memory: it habituates, anticipates periodic events, and encodes spatial information in its tubular network, thickening used channels and pruning unused ones (Kramar & Alim, 2021). Memory is not mystical—it is the retention of a signal's effect after the signal dissipates, requiring a signaling event, a structural change in response, and persistence of that change such that future behavior is modified. Every organism that displays memory is one that signals. *Physarum*'s repertoire alone—chemotaxis, allorecognition, resource optimization, anticipation, habituation, pharmacological sensitivity—in an organism with no neurons or synapses, is direct evidence that chemical signaling is the ancestral mechanism of biological information processing. The reclassification simply pushes that conclusion back by 1.5 billion years.

6 The Fruiting Body and the Concentration Signature

A persistent confusion conflates the mushroom with the organism. The organism is the *mycelium*—the distributed network permeating soil, wood, dung, or roots, the feeding and exploratory body, persisting for years to millennia. The mushroom is the *sexual organ*, existing to produce and disperse spores, grown rapidly from resources mobilized across the network and concentrated at initiation points. Its construction demands extraordinary coordination: detecting environmental thresholds, integrating them across a network with no central processor, selecting sites, routing resources, and orchestrating a differentiated three-dimensional structure in a compressed window. It is the most coordination-intensive event in the organism's life cycle.

6.1 Concentration Where Coordination Demand Is Greatest

Cultivators have long known that immature, unopened-cap specimens are more potent per unit weight than mature ones—decades of anecdote, now measured. Windsor et al. (2025) found psilocybin and psilocin concentration per gram dry weight decreasing consistently from veil-intact buttons

to mature, uplifted-cap specimens across four *Psilocybe* species. The mechanism is understood: Demmler et al. (2020) showed *psiD*, the gateway enzyme gene, upregulated 395-fold in primordia relative to vegetative mycelium, with expression already declining by maturity. The organism front-loads biosynthesis into the earliest, most rapidly developing phase, and the alkaloid pool is then diluted as the structure expands.

This distribution is consistent with a coordination signal: signaling molecules concentrate where and when coordination demand is highest—neurotransmitters at synapses, growth factors at wound margins, cytokines at sites of immune activation. That psilocybin peaks during construction of the reproductive organ, the most coordination-intensive event in the life cycle, is the pattern the signaling conjecture predicts.

Honesty requires one qualification, developed more fully in the companion chemical-ecology paper. This concentration gradient is *consistent with* a signaling role but does not by itself *discriminate* signaling from defence, because an optimal-defence allocation predicts much the same distribution: the young, rapidly developing, reproductively critical primordium is exactly the tissue an optimal defender should protect most. The gradient is therefore strong supporting context, not a decisive line. What discriminates the accounts is the *temporal* question—whether biosynthesis *precedes* the morphological transitions it is hypothesised to coordinate (signaling) or merely tracks tissue value at each moment (defence)—and that test is named below and taken up in the companion paper.

6.2 Why the Primary Function Is Unlikely to Be Defence

The default assumption in much of the literature is that psilocybin is a chemical defence against predation. Under the multifunctionality principle, the right question is not whether it has *any* defensive role—it may, as a secondary or exapted function—but whether *defence is its primary, ancestral function*. On present evidence, that is unlikely, for two reasons.

First, when fungi build a primary chemical defence, they do not equivocate. *Amanita phalloides* and *Galerina marginata* produce amatoxins that destroy hepatocytes (a single cap can kill an adult); *Cortinarius* species produce orellanine, an irreversible nephrotoxin. These attack core metabolic machinery and kill what eats them—unambiguous in function. Psilocybin does none of this: it is non-toxic at any natural dose.

Second, it fails the basic test of a defence—it does not deter the organisms that actually eat the mushroom. Wild *Psilocybe* are routinely colonized by insect larvae and grazed by gastropods, and insects are reared to adulthood from psilocybin-containing tissue (Bradshaw et al., 2024). Meyer and Slot (2023), in the most comprehensive ecological review to date, concluded that empirical evidence for any specific ecological role is largely lacking and that speculation dominates the question. The defence framing is a persisting default, not an established finding—it held its place because no rival was rigorously tested against it.

The conjunction is what matters: in a lineage demonstrably capable of producing lethal deterrents when selection favours them, psilocybin is conspicuously not one, and it engages a *signaling* receptor rather than a metabolic target. This does not exclude a secondary defensive or anti-palatability role—multifunctionality permits one—but it makes signaling, not defence, the more parsimonious *primary* function. (Note that the signaling reading requires only that fungal signal reception may operate through architecture distinct from the mammalian serotonin receptor; convergent and divergent molecular solutions to one functional problem are routine, and fungi demonstrably do receive chemical signals, or they could not coordinate the behaviors observed.)

7 Implications for the Clinical Framework

The clinical contributions of Paper One—the dual-drift model, the five-step grounding framework, the psychosis-differentiation criteria—are unaffected by this paper. They are clinical tools grounded in observation and established neuroplasticity science, and their validity does not depend on the mechanistic conjecture.

What this paper changes is the depth of the conjecture beneath them. The signaling reading no longer begins with fungal indolamine production; it begins with the selection of tryptophan as a signaling precursor in the last common ancestor of Amoebozoa and Opisthokonta. On this view, psilocybin is not an alien molecule intruding on the human serotonergic system but a molecular cousin—separated by elaboration, united by ancestry—returning to a receptor architecture built to recognize molecules like it. Whether and how that deep-kinship reframe (from "introducing a foreign substance" to "engaging an ancestral signaling architecture") should inform clinical practice is left to the facilitator's judgment, and it is offered as perspective, not as clinical instruction.

8 Open Questions Handed Forward

The principal open questions this paper raises, for colleagues with the tools to answer them:

1. **Identify *Physarum*'s signaling molecule (the cleanest test).** Alim et al. demonstrated a nutrient-triggered coordinating signal of unknown identity. The conjecture predicts it is tryptophan-derived. Direct chemical identification would confirm or refute this outright, and it is technically tractable now.
2. **Date the recognition architecture.** How far back does tryptophan-derivative receptor recognition actually extend? Comparative receptor phylogenetics across Amoebozoa, fungi, animals, and plants would test whether the recognition machinery is genuinely ancestral to the supergroup split, as the hierarchy in Section 4 proposes.
3. **Temporal precedence (the discriminating test).** Does psilocybin biosynthesis *precede* the morphological transitions of fruiting (signaling) or follow them (byproduct or defence allocation)? Time-resolved measurement through fruiting initiation would settle the question the static concentration gradient cannot.
4. **The fungal receptor.** Through what architecture do fungi themselves receive indolamine signals? Identifying the fungal receptor(s) would convert the signaling conjecture from inference to mechanism, and would test whether reception is conserved alongside production.
5. **Primary versus secondary function.** Does psilocybin have any measurable defensive or anti-palatability role, and if so is it ancestral or exapted? The multifunctionality principle predicts a repertoire; characterizing it, and ordering it by primacy, is the central open problem the corpus poses.

9 Conclusion

The reclassification of *Physarum polycephalum* from fungi to Amoebozoa does not weaken the mycelial-signaling conjecture; it deepens it. The mechanism proposed in the parent paper—indolamine signaling within fungal networks—is revealed as one chapter in a longer story. Tryptophan-based signaling architecture was established before fungi, animals, or nervous systems

existed; the major eukaryotic lineages inherited the toolkit and elaborated it independently; and the cross-kingdom receptor compatibility that lets psilocybin engage the mammalian serotonin system is molecular inheritance from a common ancestor roughly 1.5 billion years old. The fruiting body concentrates psilocybin where coordination demand is greatest—consistent with a signal, though not by itself decisive against defence—while the lineage's genuine defences kill and deter and psilocybin does neither, making signaling the more parsimonious primary function. Living systems have inner states; they navigate, discriminate, remember, and signal—and the molecule at the root of that signaling, from the earliest amoebozoan to the mammalian brain, is tryptophan. These claims are conjecture with named tests, in a field that prohibition kept thin and is only now open to filling.

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