Redacted Science Research Initiative

Paper Seed Master

Jim Craddock | #TheArchitect

redactedscience.org | jimcraddock.com

Version 6 | Last revised: 20260425 (Seed 017 Source, New Seed 018)

Keywords: #TheArchitect, Paper Seed Master, Redacted Science Research Initiative

Document Purpose and Usage Instructions

What This Document Is

This document contains seed outlines for papers to be generated within the Redacted Science Research Initiative. Each seed is a structured prompt sufficient for an AI instance with access to the project corpus to generate a first-draft paper.

Version 5 changes the structural organization from series-grouped to flat-table-ordered. Each seed carries a three-digit primary key number assigned at insertion. The series prefix is a mutable attribute, not a numbering scheme. Seeds are ordered in the document by insertion order. The first seed inserted is Seed 001; new seeds append to the end.

Data Model

The Seed Master functions as a flat table. Each seed is one row. The row's primary key is its three-digit number, permanent from insertion forward. Attributes on the row (series, template, maturity, publication target, last-revised date) are mutable. Seeds may be reclassified (series changed) without affecting the primary key. Seeds that never advance to publication retain their number in the document as intellectual record of what was considered.

The primary key has three design properties: (1) it identifies the seed unambiguously across time, (2) it survives reclassification, and (3) it does not encode semantic information about the seed. A researcher citing "Seed 001 of the Paper Seed Master" retrieves exactly the intellectual object Endometriosis represents, regardless of what series attribute the seed carries at the moment of citation.

Current State of Seeds:

This document is meant as an index of ideas with relational data that expands upon those ideas. Therefore, some ideas are merely at the idea stage, while others are more developed. This is by design. Some ideas may never be completed by the Architect. That does not preclude them from being advanced

by someone else, however, the master list of Architect built reports is held at:
https://jimcraddock.com/redacted-science-compilation.html

Numbering Rule

- Numbers are assigned at insertion and never change.
- Numbers are three-digit with leading zeros (001, 002, 017). Leading zeros are never truncated.
- Numbers reflect insertion order, not series organization.
- A new seed receives the next available number and appends to the document.
- If a seed is retired or marked stale, the number remains occupied; it is not reassigned.
- Not all seeds get written. Unwritten seeds still occupy their number as intellectual record.

Architect Report Numbering vs. Seed Numbering

Architect Reports track publications; the Seed Master tracks seeds. The two numberings are separate and will diverge permanently. Some seeds generate multiple Architect Reports (V1, V2 revisions). Some generate companion deposits (Clear Evidence argument paper plus protocol). Some generate none. The Architect Report Registry at jimcraddock.com/architect-reports documents every issued report and which seed it derived from.

Grandfathered note: A#002 V1 and V2 (Endometriosis) were published under the pre-v5 Architect Report designation convention and retain that designation for stability of the public record. All Architect Reports issued from v5 forward adopt the full series-prefix-plus-version convention..

Who This Document Is For

Primary user: Jim Craddock, Redacted Science, operating with AI assistants (primarily Claude and Grok).

Secondary users: Any AI instance opening this document to work a seed. Any future human collaborator who joins the project.

Framework Primer (canonical short-form summary)

The three-paragraph canonical summary below may be adapted (not copied verbatim) by an AI instance generating a paper's introduction. All seed-derived papers should carry a framework summary that matches the voice and substantive content of this primer; variance across outputs should be minimized.

Paragraph 1. The Redacted Science framework proposes that *Candida albicans* functions as a coevolved biochemical computer in its mammalian hosts, operating a distributed governance system over host physiology through the endocannabinoid interface, the perfusion architecture of the pituitary, and the substrate metabolism of multiple organ systems. The organism is not a pathogen in the conventional sense but a commensal regulator whose activity shapes host biochemistry at every documented timescale from moment-to-moment substrate management to lifelong phenotype expression. Paper A (Craddock, Biochemical Computer) establishes this core model.

Paragraph 2. The Saline Oscillation Hypothesis (Craddock, Saline Oscillation) places the framework in evolutionary context: the organism-host partnership coevolved under the Plio-Pleistocene salinity oscillations of the East African Rift System, selecting for symbiont capability to manage host electrolyte balance, perfusion, and stress response during environmental pressure. This produces the *Homo candidus* phenotype the framework recognizes as ancestral and, in the Pan-Mammalian extension, generalizes to *Mammalia candidus* across the mammalian clade.

Paragraph 3. Under this framework, many chronic conditions of modern medicine map onto stuck program modes of the organism-host governance system. The Umbrella Paper (Craddock, Stuck-State Umbrella) articulates the stuck-state model. The framework predicts that conditions currently treated symptomatically will respond differently when the organism layer is recognized and addressed, and that population-level patterns in chronic disease epidemiology reflect organism-host relationship disruptions rather than purely host-side dysfunctions.

Required Context Before Working Any Seed

An AI instance new to the project must review the following before attempting to draft a seeded paper.

The Three Foundational Papers

- **Paper A —** *Craddock, Biochemical Computer* — DOI: 10.5281/zenodo.19337525.
- **Paper B —** *Craddock, Saline Oscillation* — DOI: 10.5281/zenodo.19369715.
- **Paper C —** *Craddock, Longitudinal Case Study* — DOI: 10.5281/zenodo.19560800.

Framework Extensions

- *Craddock, Pan-Mammalian Hypothesis* — DOI: 10.5281/zenodo.19643601.
- *Craddock, Implications of Biochemical Computer* — DOI: 10.5281/zenodo.19488041.
- *Craddock, Focal Infections 2.0* — DOI: 10.5281/zenodo.19423069.
- *Craddock, Exposé* — DOI: 10.5281/zenodo.19393803.

Clinical Case Reports

- *Craddock, Acute Hemodynamic Decompensation* — DOI: 10.5281/zenodo.19462705.

Clear Evidence, No Trial Series

- *Craddock, Clear Evidence IBS* — DOI: 10.5281/zenodo.19645403.
- *Craddock, Clear Evidence IBS Protocol* — DOI: 10.5281/zenodo.19646550.

Stuck-State Series

- *Craddock, Stuck-State Umbrella* — DOI: 10.5281/zenodo.19582484.
- *Craddock, T2D Stuck State* — DOI: 10.5281/zenodo.19582791.
- *Craddock, Obesity Stuck State* — DOI: 10.5281/zenodo.19600443.
- *Craddock, Anorexia Stuck State* — DOI: 10.5281/zenodo.19583423.
- *Craddock, IBS Stuck State* — DOI: 10.5281/zenodo.19598460.
- *Craddock, Parkinson's Stuck State* — DOI: 10.5281/zenodo.19600888.

Architect Reports

- *Architect Report A#002 V2 — Endometriosis as Organism-Directed Tissue Recruitment* — (generated from Seed 001). Grandfathered under pre-v5 convention.

Zenodo community: zenodo.org/communities/redactedscience/. Search: metadata.creators.person_or_org.name:"Craddock"

Core Vocabulary Used Across All Seeds

Biochemical computer; version conflict; interface error; stuck program mode; Homo candidus; Mammalia candidus; phase transitions; quorum sensing; saline oscillation; TODIC (Terminal Onset Diabetes

Insipidus with Candidosis); feeding mechanism; overflow-retrieval cycle; pituitary override; net-output reframe; organism-managed architecture; governance load.

Series Attribute Values

The series attribute on each seed takes one of the following values. Series does not determine seed number; it is a classification tag for downstream filtering, registry organization, and Architect Report designation.

- **AM** — Mechanism. Specific biochemical, anatomical, or behavioral mechanisms operating under the framework.
- **AS** — Stuck State. Chronic conditions under the Umbrella paper's stuck-program-mode model.
- **AB** — Substance (AB for suBstance). Dietary inputs, pharmaceuticals, environmental compounds interacting with organism-host governance.
- **AI** — Autoimmune Collateral. Conditions conventionally classified as autoimmune, reframed as organism-directed immune activity.
- **AH** — Historical/Institutional. Suppression, regulatory capture, institutional self-preservation patterns. The Exposé paper anchors this series.
- **AO** — Observational. Case studies, longitudinal observations, family-relative and cross-host observations.

Voice and Style Requirements

All seeded papers follow the three-voice framework:

1. Academic voice for cited literature and formal scientific claims.
2. Storytelling voice for framework narrative and mechanism explanation.
3. #TheArchitect bracketed asides for lived authority and editorial commentary. Reserved for framework papers. NOT used in Clear Evidence series entries.

Additional standing requirements: no em dashes (AI writing tell); "coevolution" one word lowercase; "Pan-Mammalian" hyphenated; C. albicans italicized consistently; Times New Roman 12pt; hanging indent references; date format YYYYMMDD with no separators.

Voice Calibration for AH Series

For papers in the AH series (Historical/Institutional), the #TheArchitect voice runs at higher density and sharper edge than in clinical framework papers. The author's 23-year Medical Informatics career provides direct institutional authority; the voice reflects that authority unapologetically.

Bracketed asides occur at approximately every 400-600 words of prose, compared to every 1200-1800 words in clinical papers. Asides in institutional papers may name economic incentives, regulatory capture, and institutional self-preservation patterns directly.

Sardonic wit may be used where the subject matter invites it. Sardonic wit lands when earned by the material: a regulator saying one thing while the public record shows another, a funding stream moving opposite to the stated mission, an economic interest hiding in plain sight inside a guideline. Sardonic wit fails when deployed at genuinely earnest actors, at patients, or as default voice rather than selective tool.

Citation Discipline

An AI instance generating a paper from a seed may cite ONLY sources in the following four categories. Citations outside these categories are flagged in a separate "Suggested additional citations" block at the end of the draft for author review rather than inserted inline.

- **(a)** Papers already in the Redacted Science Research Initiative corpus, cited by author-short-title format (see Citation Convention below).
- **(b)** Peer-reviewed citations specified in the seed's Existing Literature Support section.
- **(c)** Non-peer-reviewed sources that themselves cite one or more Redacted Science Research Initiative papers, with traceable citation trail, clearly identified as non-peer-reviewed.
- **(d)** Other Architect Reports, identified by their canonical designation (series prefix, number, version suffix), Zenodo DOI, and Registry entry.

Citation Convention

Cite RS foundational papers using author-short-title format inline. Prose references to "Paper A / Paper B / Paper C" are acceptable within sentences.

Inline citation examples:

- (Craddock, Biochemical Computer) — for Paper A
- (Craddock, Saline Oscillation) — for Paper B
- (Craddock, Longitudinal Case Study) — for Paper C
- (Craddock, Stuck-State Umbrella; Craddock, IBS Stuck State) — multiple RS citations

Do NOT use year-letter suffix format such as (Craddock, 2026a). This format is deprecated.

Output Format Requirements

First draft of any seeded paper is delivered as a single document with the following standard sections in order:

4. Abstract (250-400 words)
5. Keywords (one term per entry, Zenodo-compatible)
6. Introduction (with adapted Framework Primer)
7. Framework Basis
8. Mechanism
9. Predictions (numbered, with evidence class)
10. Discussion
11. Counter-Arguments Addressed
12. Conclusion
13. Closing Declaration
14. References (hanging-indent, alphabetized)
15. Suggested Additional Citations (if any)

What a Seed Is Not (failure mode prevention)

- Not a literature review (unless Review publication target is specified)
- Not a pre-registered protocol (unless Clear Evidence Protocol companion is specified)
- Not a case report (unless Case Report publication target is specified)

- Not a textbook chapter or general framework introduction
- Not a clinical practice guideline or treatment recommendation

Maturity Upgrade Checklist

A seed advances from developing to ready-to-draft only when all of the following are true:

16. The Claim field contains a single-sentence testable claim.
17. The Framework Basis field points to specific foundational paper content.
18. The Mechanism field is articulated in 2-4 paragraphs.
19. At least three Predictions are specified with Evidence Class.
20. At least three Existing Literature Support entries are identified.
21. At least three Counter-Arguments are drafted with Responses.
22. Publication Target is selected.
23. What This Seed Is NOT boundaries are explicit.

Failure Modes to Watch For in AI-Generated Output

- **Loss of framework voice.** Reverts to textbook medical writing.
- **Invented citations.** Any citation not falling in categories (a)-(d).
- **Over-hedging.** "Might be suggested," "some have speculated."
- **Missing Architect voice.** Framework papers should carry bracketed asides; Clear Evidence should not.
- **Cut or underweight counter-arguments.** Verify substantive responses present.
- **Confabulated specific values.** Dates, lab values, DOIs not in seed or corpus.
- **Framework primer copied verbatim.** Primer is for adaptation, not copy-paste.
- **Wrong citation format.** Year-letter suffix instead of author-short-title.
- **Missing Keywords section.** Mandatory under v4 forward.
- **Missing version suffix on Architect Report designation.** Initial issuance is V1.

Architect Report Authentication Architecture

All papers generated through the Redacted Science Seed Analysis Process are issued as Architect Reports under their series prefix. The Architect Report Registry at jimcraddock.com/architect-reports is the authoritative source; each entry lists series prefix, number, version, Zenodo DOI, Nostr event ID, and SHA-256 hash of the canonical PDF.

Closing Declaration Template

> *This Architect Report [PREFIX#NNN V#] was generated through the Redacted Science Seed Analysis Process, from Seed [NNN] of the Paper Seed Master, under the Redacted Science Research Initiative. Issued [date] by Jim Craddock, #TheArchitect. Authenticity verifiable at jimcraddock.com/architect-reports. Papers claiming any A-series designation not listed in the registry are not authentic Architect Reports.*

Footer Format

Seed Test-Run Procedure

24. Verify seed maturity is ready-to-draft.
25. Load the full project (framework corpus plus this master) into the AI instance.
26. Paste seed content and the instruction: "Generate a first draft of this paper per the Redacted Science voice and style requirements in the Paper Seed Master. Use the framework corpus in context. Cite only per Citation Discipline categories (a)-(d) using the author-short-title format. Produce output with all required sections including Keywords, footer, closing declaration, and V1 version suffix."
27. Expected first-draft length: 3000-6000 words standard; 1500-3000 words Clear Evidence; 4000-8000 words substantial mechanism.
28. Run the Failure Mode checklist against the output.
29. Zero-one failure: accept for editorial pass. Two-three: request regeneration. Four+: revise seed or master.
30. Update seed status with draft date, AI instance, failure count.
31. Editorial pass; Zenodo deposit; Registry update; Nostr issuance.

The Three Seed Templates

Each paper type asks a different question. Use the template that matches the question the paper answers.

- **Template A — Condition:** claims about a named disease, chronic condition, or syndrome mapping onto the framework.
- **Template B — Substance:** claims about a substance, compound, dietary input, drug, or exposure.
- **Template C — Mechanism:** claims about a specific biochemical, anatomical, or behavioral mechanism.

Template A: Condition Seed

```
## Seed NNN: [Condition name]  [Series: AS | AI | AO | etc.]
**Template:** A (Condition)
**Maturity:** [seed | developing | ready-to-draft]
**Last revised:** YYYYMMDD
**Publication target:** [specific]

### Claim (one sentence)
### What this seed is NOT
### Framework basis
### Conventional understanding and its gaps
### Mechanism (framework reading)
### Predictions (numbered, with evidence class)
```

```
### Existing literature support
### Counter-arguments to address
### Related existing Redacted Science work
### Notes and observations
### Status
```

Template B: Substance Seed

```
## Seed NNN: [Substance name]  [Series: AB]
**Template:** B (Substance)
**Maturity:** [seed | developing | ready-to-draft]
**Last revised:** YYYYMMDD
**Publication target:** [specific]

### Claim (one sentence)
### What this seed is NOT
### Framework basis
### Substance characterization
### Organism-direct effects
### Host-system effects
### Population-level signature
### Predictions (numbered, with evidence class)
### Existing literature support
### Counter-arguments to address
### Related existing Redacted Science work
### Notes and observations
### Status
```

Template C: Mechanism Seed

```
## Seed NNN: [Mechanism description]  [Series: AM]
**Template:** C (Mechanism)
**Maturity:** [seed | developing | ready-to-draft]
**Last revised:** YYYYMMDD
**Publication target:** [specific]

### Claim (one sentence)
### What this seed is NOT
### Framework basis
### Mechanism (core description)
### Anatomical or physiological sites involved
### Evidence already in the corpus
### Predictions (numbered, with evidence class)
### Existing literature support
### Counter-arguments to address
### Related existing Redacted Science work
```

```
### Notes and observations
### Status
```

Seed Table

Seeds are listed in insertion order. Each seed carries a permanent three-digit primary key. Series attribute is mutable; primary key is not.

Seed 001: Endometriosis as Organism-Directed Tissue Recruitment *[Series: AS]*

Template: A (Condition)

Maturity: PUBLISHED as Architect Report A#002 V2 (grandfathered designation). Seed remains available for future revisions. Nostr Event ID: 1dff01ce8d66aeb89d41de6588aa8eb3fd77162db44f3eb981352dd98963a9bf

Publication target: Stuck State series entry; Clear Evidence companion protocol candidate.

Claim: Endometriosis represents a Stuck State in which C. albicans-directed tissue recruitment produces ectopic endometrial establishment and maintenance at sites the organism has colonized, with the menstrual-cycle symptom pattern reflecting organism response to cyclic hormonal substrate availability.

Full seed content carried in Architect Report A#002 V2 and the Zenodo deposit. Paper available at 10.5281/zenodo.19718491 (verify exact version DOI at Registry).

Seed 002: ApoB/LDL Net-Output Reframe *[Series: AM]*

Template: C (Mechanism)

Maturity: developing (priority for next ready-to-draft advancement)

Publication target: Zenodo AM# framework paper

Claim: Serum LDL-C is best understood as the net equilibrium between hepatic production, receptor-mediated clearance, and organism-directed consumption, rather than as a direct measure of host-side lipid metabolism alone. This net-output framing parallels the pituitary hormone reframe applied elsewhere in the framework.

Framework basis: (Craddock, Biochemical Computer) for organism substrate management; (Craddock, Longitudinal Case Study) for the 12-year linear cholesterol trajectory at 4.0 mg/dL per year anchoring the observation; (Craddock, Saline Oscillation) for coevolutionary positioning.

Mechanism: Conventional LDL measurement treats serum value as output of hepatic production and peripheral uptake. Under the framework, a third variable operates at continuous scale: organism consumption of LDL particles as substrate, and organism signaling that modulates hepatic production of ApoB-containing particles. Wang et al. (2024) documented direct organism-mediated LDL-C elevation via formyl-methionine, HIF-2α activation, and ceramide synthesis. Dell'Olmo et al. (2021) identified antifungal cryptide peptides embedded in ApoB itself.

Predictions: (1) Framework-positive subjects show less LDL-C variance and more linearity than framework-negative subjects matched for age/diet. (2) Antifungal intervention produces LDL-C decreases

within 4-8 weeks correlated with baseline mycobiome markers. (3) ApoB/LDL-C ratio differs between framework-positive and framework-negative subjects.

Literature support: Wang et al. (2024, Cell Host & Microbe); Dell'Olmo et al. (2021, AMB, 105(5), 1953-1964). Status: developing; highest priority for next advancement.

Seed 003: Quorum Sensing as Stuck-State Clustering Mechanism (with cross-kingdom QS) *[Series: AM]*

Template: C (Mechanism)

Maturity: developing

Publication target: Zenodo AM# framework paper

Claim: Chronic disease clustering (metabolic syndrome, autoimmune clusters, psychiatric-GI comorbidity, reproductive-GI comorbidity) is produced by quorum sensing between C. albicans and the bacterial microbiome it co-governs, not by the fungal organism alone. Cross-kingdom QS (documented between Pseudomonas aeruginosa and C. albicans; Fourie & Pohl 2019 review) extends the framework's governance model to include bacterial partners as coordinated state-change executors.

Status: developing; needs Hogan 2006 literature and Fourie-Pohl review integration.

Seed 004: Adult-Onset Weight Gain Transition *[Series: AS]*

Template: A (Condition)

Maturity: developing (priority advancement candidate)

Publication target: Stuck State series companion to Obesity Stuck State; Substack public-audience essay companion

Claim: Adult-onset weight gain without clear dietary or activity change represents an organism governance threshold crossing event rather than a metabolic slowdown, with specific predictive markers distinguishing the transition event from sustained obesity.

Pairs with the existing Obesity Stuck State paper but focuses on the transition event. Strong public-audience potential.

Seed 005: Recurrent Aphthous Stomatitis (Canker Sores) *[Series: AS]*

Template: A (Condition)

Maturity: seed

Claim: Recurrent aphthous stomatitis represents chronic low-level mucosal C. albicans activity producing ulcerative tissue breakdown at local pH-disruption points (acidic foods, mechanical trauma). The conventional literature has no strong etiology; the framework reads it as a mucosal-compartment stuck state.

Seed 006: Chronic Rhinosinusitis with Aspergillus Co-Colonization *[Series: AS]*

Template: A (Condition)

Maturity: seed

Claim: Chronic rhinosinusitis with aspergillus culture positivity represents a primary C. albicans governance failure in the sinus compartment producing chronic inflammation, with Aspergillus arriving as secondary colonizer in the compromised niche. Repeated surgical drainage without antifungal coverage perpetuates the pattern. Distinct from AFRS but mechanistically related.

Seed 007: Dietary Sulfur Withdrawal as Stuck-State Destabilizer

[Series: AB]

Template: B (Substance)

Maturity: developing

Publication target: Clear Evidence, No Trial series entry with companion pre-registered protocol

Claim: Dietary sulfur-amino-acid withdrawal, specifically through cessation of habitual egg consumption, can destabilize an organism-host governance architecture in individuals whose biochemistry has calibrated to a sustained sulfur input, producing decompensation events whose timing and character the stuck-state framework predicts and that standard nutritional medicine does not recognize as diet-related.

Framework basis: (Craddock, Biochemical Computer) general framework of organism-managed host biochemistry extended to sulfur amino acid substrate class; (Craddock, Longitudinal Case Study) 2021 decline cluster with two-egg breakfast cessation as contributor; (Craddock, Stuck-State Umbrella).

Key literature: Miller et al. (2005, Aging Cell); Wang et al. (2024); Dell'Olmo et al. (2021). Status: developing; needs methionine restriction trial and egg cessation cohort literature search.

Seed 008: HFCS as Population-Scale Substrate Availability Event

[Series: AB]

Template: B (Substance)

Maturity: developing

Publication target: Zenodo framework paper with Substack companion essay; Clear Evidence entry candidate

Claim: High-fructose corn syrup, introduced at scale into the US food supply beginning in the 1970s, constitutes a population-scale substrate availability event for the resident C. albicans symbiont population, whose shifted metabolic activity and host-governance output produced the epidemiological signatures (T2D, NAFLD, obesity, metabolic syndrome) that mainstream medicine attributes to caloric or macronutrient effects alone.

Substance characterization: HFCS-42/HFCS-55, corn-derived, introduced 1970, widespread 1978-1984. US per-capita rose from ~0 in 1970 to ~60 lbs/person/year by 2000. Unbound monosaccharides in aqueous solution produce faster fructose uptake and different distal-bowel substrate availability than caloric-equivalent sucrose.

Key literature: Bray et al. (2004, AJCN); Lustig; Tappy; Wang et al. (2024); Dell'Olmo et al. (2021); Mexico sugar-tax natural experiment (2013 onward).

Seed 009: Proton Pump Inhibitors in Framework-Positive Patients

[Series: AB]

Template: B (Substance)

Maturity: seed (priority)

Claim: Long-term PPI use in framework-positive patients accelerates organism expansion by removing the gastric acid ecological constraint, producing higher rates of chronic disease transitions than matched controls. Widespread chronic medication (tens of millions of US patients). Strong Clear Evidence companion candidate.

Seed 010: Doxycycline and Tetracycline-Class Antibiotics *[Series: AB]*

Template: B (Substance)

Maturity: seed

Claim: Doxycycline and tetracycline-class antibiotics accelerate fungal expansion in framework-positive patients by eliminating bacterial competitors, with the drug's anti-inflammatory effect (matrix metalloproteinase inhibition) masking the visible signal while worsening underlying architecture. Particularly relevant in chronic fungal sinusitis, where the drug is frequently prescribed.

Seed 011: Turmeric and Curcumin Formulation Variability *[Series: AB]*

Template: B (Substance)

Maturity: seed

Claim: The observation that identical active compound (curcumin) produces different symptomatic responses across commercial preparations suggests that preparation process, carrier compounds, or contamination interact with organism ecology rather than the compound itself operating in isolation. Testable via multi-brand N-of-1 observational protocol.

Seed 012: Autoimmune Collateral Umbrella Paper *[Series: AI]*

Template: A (Condition, umbrella)

Maturity: developing (foundational for series)

Publication target: Zenodo AI series anchor paper

Claim: Conditions conventionally classified as autoimmune represent collateral effects of organism-directed tissue recruitment, organism-mimetic antigen presentation, and organism-protective immune redirection, rather than spontaneous host-self-attack. The umbrella paper establishes the mechanism class and provides the framework scaffold for individual condition papers under the series.

Structural parallel to Umbrella Stuck State paper.

Seed 013: Celiac Disease as Framework-Positioned Autoimmunity *[Series: AI]*

Template: A (Condition)

Maturity: developing (priority; Dr. Bath audience)

Claim: Celiac disease represents autoimmune collateral of organism-host mucosal governance failure in the HLA-DQ2/DQ8 genetically predisposed host, with the gluten-tTG-deamidation cascade providing the antigenic hook while the organism layer explains differential penetrance of the same HLA type across populations and individual lifespans.

Framework basis includes Akbari et al. (likely gluten-Neolithic transition literature, verify citation); Th1/Th2 balance literature; HLA-DQ2/DQ8 penetrance data; celiac-thyroid-endometriosis comorbidity clusters.

Seed 014: Hashimoto's Thyroiditis as Framework-Positioned Autoimmunity *[Series: AI]*

Template: A (Condition)

Maturity: developing

Claim: Hashimoto's thyroiditis represents autoimmune collateral of organism-directed activity at the thyroid compartment, with the iodine-sensitive nature of both thyroid metabolism and C. albicans providing the compartment-specific interface. Strong female skew, pregnancy-onset patterns, and GI-reproductive comorbidity clusters are consistent with organism governance shifts.

Seed 015: CDC/MMWR Suppression Case *[Series: AH]*

Template: C (Mechanism, institutional variant)

Maturity: seed

Claim: A specific documented instance of data suppression in contemporary CDC/MMWR practice demonstrates that the institutional-erasure mechanism documented historically in the Exposé paper operates in modern form. Tracks the specific suppression event (to be specified from author's working notes), the institutional actors involved, the public record inconsistencies, and the downstream consequences for affected researchers and patient populations.

Voice calibration: AH series — sardonic wit permitted where material invites it. Architect asides at higher density than clinical papers.

Seed 016: DSHEA Regulatory Barrier and the Lemon Balm Example *[Series: AH]*

Template: C (Mechanism, institutional/regulatory/economic variant)

Maturity: seed

Claim: The 1994 Dietary Supplement Health and Education Act (DSHEA) prevents grocery-available compounds with documented antifungal, anxiolytic, and AChE inhibitor properties from being marketed for therapeutic purposes, creating a structural economic barrier between cheap functional interventions and the pharmaceutical markets they would compete with. Lemon balm serves as the concrete example (antifungal; anxiolytic via GABA receptor activity; AChE inhibitor with documented cognitive effects) covering approximately $22B in combined pharmaceutical market equivalents.

Strong public-audience potential. Substack companion feasible.

Seed 017: Autism Spectrum Disorder as Developmental Stuck-State

[Series: AS]

Template: A (Condition) — with AI series overlap for Trajectory A immune-activation subgroup

Maturity: ready-to-draft for all three deployment paths (SHANK3-subtyped, Clear Evidence No Trial companion, full-spectrum autism). Remaining literature gaps are now non-blocking and can be addressed within the papers.

Publication target: Stuck State series entry as full Architect Report; SHANK3-subtyped first deployment as shortened paper; Clear Evidence No Trial companion (NCT00936182) as independent deployment

Claim

Autism spectrum disorder represents stuck-state program execution within critical developmental windows, where outcome phenotype is determined not by distinct underlying mechanisms but by the timing of stuck-state onset relative to ongoing neurodevelopment, with two distinguishable trajectories (perturbation-triggered regression from typical development; early-locked development from prenatal or perinatal stuck-state establishment) producing the heterogeneity the autism spectrum displays.

What this seed is NOT

This seed is not a review of autism spectrum disorder literature. It is not a clinical practice guideline. It is not a treatment protocol. It is not a claim about any single cause of autism. It is not a claim that vaccines cause autism. It is not a claim that antifungal therapy is a universal treatment for autism. It is a framework paper proposing a specific stuck-state mechanism that may operate across a subset of autism presentations, generating testable predictions that would identify which subset and which interventions are framework-responsive.

Framework basis

- (Craddock, Biochemical Computer) — organism cross-kingdom signaling access to neurological, immune, GI, autonomic, and endocrine interfaces.
- (Craddock, Saline Oscillation) — coevolutionary framework; developmental windows as substrate-surface events.
- (Craddock, Stuck-State Umbrella) — stuck program mode model; this seed extends the model into neurodevelopmental disorder.
- (Craddock, IBS Stuck State) — structural template for bowel-comorbidity reading.
- (Craddock, Pan-Mammalian) — vertical symbiont transmission as contributor to apparent heritability.

The Two-Trajectory Model (core seed contribution)

Trajectory A — Perturbation-Triggered Regression. Typical development proceeds for months or years. A perturbation event (antibiotic exposure, infection, immune activation, dietary shift, environmental trigger, hormonal transition) pushes the system into a stuck state. Clinical expression more often includes retained cognitive infrastructure (higher representation in high-functioning presentations). Imaging shows visible event signature.

Trajectory B — Early-Locked Development. Stuck state established prenatally or in the first months of life. Gut-brain axis, immune calibration, sensory integration, myelination develop around the altered signal set. Clinical expression tends toward broader developmental delay. Imaging reads as fewer abnormalities because measurement baseline is atypical-as-default.

Back-Explanation of the Rochat Paradox: Rochat et al. (2020) found HF > DD imaging abnormalities in ASD under 5, paradoxical under conventional models. Under the two-trajectory model the finding is predicted.

Preclinical and Clinical Validation of Trajectory A

Trajectory A now has independent clinical and preclinical validation.

Clinical: Sandler et al. (2000) treated 11 regressive-onset autistic children with oral vancomycin, showing significant improvement in behavior and communication (P=.003 on both), with behavioral deterioration within two weeks of discontinuation and return toward baseline across 2-8 month follow-up. Fecal analysis revealed absent Peptostreptococcus species and anaerobic cocci in all four children sampled, contrasting with 93% presence at approximately 10% of stool microorganisms in 104 adult controls. The authors explicitly proposed a gut-brain connection with neurotoxin-producing opportunistic bacteria as the mechanism, drew parallels to infant botulism and C. difficile colonization, and flagged autoantibody literature as a potential infectious-trigger pathway. The 2000 paper framed the full framework position and documented its central predicted ecological signature. The field did not systematically pursue it.

Preclinical: Qiao et al. (2026) showed that Shank3 haploinsufficient mice (Sh3+/-) exhibit no baseline autism phenotype. Systemic LPS challenge produces motor impairment, anxiety-like behaviors, and excessive grooming approaching the homozygous phenotype. Anti-inflammatory treatment partially rescues. Transcriptomic analysis shows upregulation of neuroinflammation-related genes and downregulation of synaptic function genes; pro-inflammatory microglial activation via TLR4; synapse engulfment. The authors explicitly frame this as a preclinical model of behavioral regression, citing the ~40% regression rate in SHANK3-associated ASD and their prior finding that immunomodulator treatments helped patients.

Framework reading: Sandler 2000 and Qiao 2026 together provide clinical and preclinical support for the Trajectory A architecture — host susceptibility plus activation event produces the locked phenotype that did not occur without the event. The activation event in Qiao was LPS (bacterial endotoxin). The activation event in the Sandler cohort was unspecified but preceded the regression. The framework predicts that organism-mediated inflammatory triggering through the same TLR4-microglia-synapse-engulfment pathway produces equivalent results, and that the Sandler finding of absent commensal anaerobic cocci represents exactly the kind of ecological disruption under which C. albicans expansion and TLR4-pathway inflammation become accessible. C. albicans is a competent producer of TLR4 ligands, a documented modulator of microglial activation state, and a direct interface for vagal and systemic inflammatory signaling. The measurement gap between bacterial-LPS trigger (demonstrated) and organism-mediated trigger (predicted) is the framework's central additional claim.

Paper 2 (Wu S. et al. 2024, Molecular Autism) independently localizes the Shank3-autism phenotype to AgRP neurons in the hypothalamic arcuate nucleus, with p38α acting as the inflammatory mediator — an anatomical site at the pituitary-hypothalamus interface directly relevant to the organism's documented governance architecture. Paper 1 (Gao et al. 2025, Translational Psychiatry) documents hippocampal NMDA receptor subtype downregulation in the R1117X homozygous model. Paper 3 (Wang et al. 2017, JCI) localizes repetitive behavior to striatopallidal indirect-pathway MSNs with DREADD-based rescue. Taken together, the four papers reconstruct a distributed-circuit model of SHANK3-ASD in which different behavioral components express from different vulnerable circuits, each of which has framework-documented organism access.

Predictions

32. Differential Candida mycobiome burden between ASD subjects and controls, with bimodal distribution within ASD. Partial retrospective validation: Adams et al. (2024); Kantarcioglu et al. (2016); Strati et al. (2017).

33. Regression history distinguishes an antifungal-responsive subgroup from non-regressive cases.
34. GI comorbidity severity correlates with antifungal response magnitude. Partial support: Adams et al. (2011) correlation at r=0.59, p<0.001.
35. Antifungal response is bimodal rather than normally distributed.
36. Maternal antibiotic exposure correlates with Trajectory B presentations in the child.
37. NCT00936182 results, if recoverable, show bimodal response in pyrosequencing-positive-yeast subset.
38. Wu MSR et al. (2024) SHANK3 mouse rescue, if baseline mycobiome measured, correlates with gut Candida burden rather than operating purely via host-directed IGF1R/lipid raft mechanism.
39. In Shank3 haploinsufficient mice, gut mycobiome burden at time of inflammatory challenge correlates with severity of regression phenotype; antifungal pretreatment attenuates the Qiao et al. (2026) LPS-triggered behavioral regression; organism bloom or dysbiosis produces the regression phenotype in the absence of LPS in the susceptible genotype. [Evidence class: preclinical replication with mycobiome covariates.]
40. The ecological disruption signature identified by Sandler et al. (2000) — specifically the absence of Peptostreptococcus species and other anaerobic cocci documented in all four tested regressive-autism fecal samples against 93% presence in 104 adult controls — should be replicable in modern regressive-ASD cohorts with current 16S and ITS sequencing methods, and absent-commensal status should correlate with C. albicans burden and antifungal-intervention response. [Evidence class: replication study with paired bacterial and fungal sequencing in regressive-ASD cohorts.]

Existing literature support

- Shaw, Kassen & Chaves (2000) — nystatin open-label in 23 children, CARS improvement p=0.037. Clinical Practice of Alternative Medicine 1(1):15-26.
- Nirmalkar, K., Patel, J., Kang, D.-W., Adams, J. B., & Krajmalnik-Brown, R. (2024). Bimodal distribution of intestinal Candida in children with autism and its potential link with worse ASD symptoms. Gut Microbes Reports https://doi.org/10.1080/29933935.2024.2358324
- Adams JB, Johansen LJ, Powell LD, Quig D, Rubin RA (2011) — GI-autism severity correlation at r=0.59, p<0.001. BMC Gastroenterology 11:22.
- Baker SM, Shaw W (2020) — single-case complete recovery with itraconazole. Integrative Medicine 19(4):20-27, PMC7572136.
- Ramirez PL et al. (2013) — antibiotic+antifungal combination. Case Reports in Psychiatry 2013:239034.
- Finegold SM, Dowd SE, Gontcharova V, et al. (2010) — pyrosequencing of fecal microflora in regressive autism. Anaerobe 16(4):444-453.
- Sandler RH, Finegold SM, Bolte ER, et al. (2000) — short-term benefit of oral vancomycin in regressive-onset autism. J Child Neurol 15(7):429-435. [11 children, all regressive-onset, mean age at onset 17.7 months (±3.4), mean age at treatment 59.9 months (±13.3). Behavior analog scale improved from baseline median 2.2 to post-treatment 5.0 (P=.003); Communication from 1.7 to 4.6 (P=.003). Blinded videotape review: 8 of 10 improved, 1 no change, 1 possibly worse. Six of 11 showed brief (1-4 days) hyperactivity within 3 days of vancomycin initiation (Herxheimer-like reaction). Substantial behavioral deterioration within 2 weeks of vancomycin discontinuation in most children; all but one returned toward baseline at 2-8 month follow-up. Quantitative fecal flora in 4 children revealed ABSENT Peptostreptococcus species and anaerobic cocci vs. 93% presence at ~10% of stool microorganisms in 104 adult controls — the

single most framework-relevant ecological finding in the ASD-microbiome literature. Authors explicitly proposed gut-brain connection and neurotoxin-producing bacteria hypothesis, drew parallels to infant botulism, C. difficile, and D-lactic acidosis. Authors speculated spore-forming organisms as relapse mechanism; framework adds that C. albicans persistence through antibacterial therapy extends the same logic to fungal population release from bacterial co-governance. Authors also flagged autoantibodies to neural proteins (NAFP, GFAP, MBP) in autism literature with infectious-trigger hypothesis. The field had the full framework available in 2000 and did not systematically pursue it.]

- Kantarcioglu AS, Kiraz N, Aydin A (2016) — Microbiota-Gut-Brain Axis: Yeast Species Isolated from Stool Samples of Children with Suspected or Diagnosed ASD and In Vitro Susceptibility Against Nystatin and Fluconazole. Mycopathologia 181(1-2):1-7. DOI: 10.1007/s11046-015-9949-3. PMID: 26442855. [Confirms Candida presence across pediatric ASD cohort with drug-susceptibility data for both nystatin (Shaw 2000 drug) and fluconazole (NCT00936182 drug).]
- Strati F et al. (2017) — altered gut mycobiome in ASD children, Candida enrichment documented.
- Rochat MJ, Distefano G, Maffei M, et al. (2020) — 117 ASD children under 5 MRI cohort; HF > DD imaging abnormalities. Brain Sciences 10(10):741.
- Hsiao EY et al. (2013) — maternal immune activation + microbiota + autism-like behavior in mouse model. Cell.
- Wang et al. (2024) — microbiome-vagus-behavior. Cell Host & Microbe, PMID 38754418.
- Wu MSR et al. (2024, preprint) — fluconazole reverses SHANK3-related autism-like deficits via lipid raft-driven IGF1R activation and prefrontal circuit remodeling. GSE313444. [Authors did not measure mycobiome.]
- Gao J, Wu S, Yang J, et al. (2025) — Comprehensive behavioral characterization and impaired hippocampal synaptic transmission in R1117X Shank3 mutant mice. Translational Psychiatry 15:274. DOI: 10.1038/s41398-025-03505-1. [Hippocampal NMDA receptor subtype downregulation; learning and memory deficits; distributed-circuit architecture.]
- Wu S, Wang J, Zhang Z, et al. (2024) — Shank3 deficiency elicits autistic-like behaviors by activating p38α in hypothalamic AgRP neurons. Molecular Autism 15:14. DOI: 10.1186/s13229-024-00595-4. [Localizes Shank3 autism phenotype to hypothalamic ARC at the pituitary-hypothalamus interface; p38α inflammatory mediator in AgRP neurons; rescue via p38α inactivation.]
- Wang W, Li C, Chen Q, et al. (2017) — Striatopallidal dysfunction underlies repetitive behavior in Shank3-deficient model of autism. J Clin Invest 127(5):1978-1990. DOI: 10.1172/JCI87997. [Repetitive grooming localized to striatopallidal indirect-pathway MSNs; DREADD-based rescue.]
- Qiao SN, Wang SE, Kim KY, et al. (2026) — Inflammation increases the penetrance of behavioral impairment in Shank3 haploinsufficiency mice — can it explain the behavioral regression in Autism? Molecular Psychiatry. DOI: 10.1038/s41380-026-03534-2. [Direct Trajectory A validation: Shank3+/- mice show no baseline phenotype; LPS challenge produces motor impairment, anxiety, excessive grooming; anti-inflammatory treatment partially rescues; microglia activation via TLR4; synapse engulfment; authors explicitly frame this as a preclinical model of behavioral regression citing ~40% regression rate in SHANK3-ASD.]
- NCT00936182 — Fluconazole in Children with ASD. Three-site double-blind, randomized, placebo-controlled RCT registered 2009. Principal investigators: Doreen Granpeesheh PhD (Tarzana, CA — Center for Autism and Related Disorders); Daniel Rossignol MD (Melbourne,

FL — International Child Development Resource Center); Brian Jepson MD (Austin, TX — Thoughtful House). Enrollment contingent on pyrosequencing-positive yeast; 30-day treatment; pre-specified behavioral outcome hypothesis. Results never published. Seventeen years of silence. Contact chain obsolete (CARD contact phone now routes to Medicare sales as of 20260424). Registered nine years after Sandler et al. (2000) had already demonstrated vancomycin-responsive regressive autism with explicit microbiome hypothesis and absent Peptostreptococcus finding; the trial was the proper rigorous test of the fungal-extension question that Sandler had framed. That the field waited nine years to design the test, then produced no results across seventeen subsequent years, is the artifact. The silence is the finding.

- Patel J, Kang DW, Adams JB, Krajmalnik-Brown R. (Year, journal/thesis status) — pediatric ASD vs neurotypical, ITS sequencing, bimodal Candida distribution in ASD, Candida-high children showed higher ATEC scores. **Direct partial validation of Prediction 1.**
- Krajmalnik-Brown lab MS thesis (June 2025, ASU) — adult ASD MTT with vancomycin pretreatment, fungal load increased post-vancomycin (selective pressure release), nine fungal taxa elevated in ASD baseline, six remained significant after GI confound exclusion. **Direct support for antibacterial-releases-fungal mechanism.**
- Laswi I, Shafiq A, Al-Ali D, et al., Bendriss G. (2021). A Comparative Pilot Study of Bacterial and Fungal Dysbiosis in NDD and GID. Microorganisms 9(4):741. DOI 10.3390/microorganisms9040741. **NDD shows distinctive fungal alpha-diversity increase; antibiotic exposure before age 3 produces greater fungal than bacterial dysbiosis. Direct partial validation of Prediction 5.**
- Retuerto M, Al-Shakhshir H, Herrada J, McCormick TS, Ghannoum MA. (2024). Analysis of Gut Bacterial and Fungal Microbiota in Children with ASD and Their Non-Autistic Siblings. Nutrients 16(17):3004. DOI 10.3390/nu16173004. **C. albicans 27.1% in ASD vs 13.2% in siblings ($p<0.055$); decreased Prevotella copri, Bacteroides fragilis, Akkermansia muciniphila, Faecalibacterium prausnitzii. Direct partial validation of Prediction 1 with sibling controls.**
- Wang LJ, Li SC, Yeh YM, et al. (2023). Gut mycobiome dysbiosis and intestinal permeability in ADHD. J Child Psychol Psychiatry. DOI 10.1111/jcpp.13779. **Increased C. albicans in ADHD; in vitro Caco-2 demonstration that C. albicans secretions increase gut barrier permeability. Mechanism support for organism-mediated systemic activation pathway.**
- Alookaran J, Liu Y, Auchtung TA, et al. (2021). Friend or Foe? A Mycobiome Evaluation in Children With Autism and Gastrointestinal Symptoms. (Journal not stated in clip — verify; DOI 10.1097/MPG.0000000000003349 suggests JPGN, Journal of Pediatric Gastroenterology and Nutrition). **Pilot N=50, binary detection methodology; reports highest Candida in ASD-without-GI (56%) vs ASD-with-GI (21%). Not framework refutation; addressed in Counter-Arguments.**
- **Ecker C, Marquand A, Mourão-Miranda J, et al. (2010).** Describing the Brain in Autism in Five Dimensions—Magnetic Resonance Imaging-Assisted Diagnosis of Autism Spectrum Disorder Using a Multiparameter Classification Approach. *J Neurosci* 30(32):10612-10623. DOI: 10.1523/JNEUROSCI.5413-09.2010. [Foundational multiparameter MRI classification paper; ASD classifier specifically distinguishes ASD from ADHD; methodological foundation for stratification.]
- **Floris DL, Wolfers T, Zabihi M, et al. (2020).** Atypical Brain Asymmetry in Autism—A Candidate for Clinically Meaningful Stratification. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging.* DOI: 10.1016/j.bpsc.2020.08.008. [Normative modeling of 352+513 ASD subjects; individual-deviation analysis reveals stepwise stratification by language

delay; methodological argument that group-mean approaches obscure heterogeneity that individual-deviation approaches reveal.]

- **Ren P, Bi Q, Pang W, et al. (2023).** Stratifying ASD and characterizing the functional connectivity of subtypes in resting-state fMRI. *Behavioural Brain Research.* DOI: 10.1016/j.bbr.2023.114458. [415 ASD ABIDE subjects; two-cluster stratification by ADI-R severity; Cluster 1 widespread connectivity disturbance; Cluster 2 nearly TD-like except for MCC-specific abnormalities; direct partial validation of the two-trajectory model's imaging predictions.]
- **Durkut M, Blok E, Suleri A, White T. (2022).** The longitudinal bidirectional relationship between autistic traits and brain morphology from childhood to adolescence: a population-based cohort study. *Molecular Autism* 13:31. DOI: 10.1186/s13229-022-00510-9 [verify]. [N=1950 cross-sectional, N=304 longitudinal across mean ages 6.2 and 13.5; autistic traits and brain morphology both stable across the developmental window with neither predicting changes in the other; authors observe "early changes in brain morphology in children with autistic symptoms that remain quite stable over time"; framework reading: co-stable phenotype-morphology is the predicted signature of an established stuck state with onset prior to first measurement.]
- **Nogay HS, Adeli H. (2024).** Multiple Classification of Brain MRI Autism Spectrum Disorder by Age and Gender Using Deep Learning. *Journal of Medical Systems* 48:15. DOI: 10.1007/s10916-024-02022-w [verify]. [Deep-learning classification yielding higher accuracy with age stratification (85.42%) than gender stratification (80.94%) or combined eight-way (67.94%); supports developmental stage as a stronger stratification axis than gender; eight-way classification accuracy drop suggests trajectory-specific rather than orthogonal subtype structure.]

Counter-arguments to address

41. Vaccines cause autism. [Response: framework does not make this claim. Immune activation events broadly can trigger stuck-state transitions in susceptible hosts. Distinct from proximate-cause claim.]
42. ~90% heritability — autism is genetic. [Response: vertical symbiont transmission plus genetic susceptibility to stuck-state locking produces heritable phenotype without single-locus causation.]
43. Regression reports unreliable. [Response: regression is Trajectory A's primary observable; Finegold (2010) already demonstrated regression-specific microbiome signatures.]
44. Spectrum heterogeneity defeats unitary-mechanism models. [Response: heterogeneity is predicted consequence of stuck-state onset timing interacting with developmental stage.]
45. Shaw 2000 never replicated. [Response: measurement-avoidance pattern is itself framework-relevant; NCT00936182 registered, apparently run, results never published.]

Notes and observations

- Two-trajectory model may eventually deserve its own standalone AM# framework paper.
- Clear Evidence No Trial companion on NCT00936182 may advance independently as framework-neutral first deployment.
- Vaccine-question handling requires explicit editorial decision in eventual Architect Report.
- Adaptive-enrichment trial design optimal for Predictions 1-4.
- Sensitivity: voice and framing require care. Recommend heavy editorial pass on any first-draft.

Gaps to close before advancing to ready-to-draft (full-spectrum version)

- Systematic MRI-in-ASD review stratified by regression history.
- Maternal antibiotic exposure to ASD risk with timing detail.

- Pediatric mycobiome normative data by age.
- Sandler vancomycin trial regression-subset re-read.
- Wu MSR (2024) SHANK3 mouse data availability — whether GSE313444 deposit includes banked mycobiome samples or whether authors deliberately did not collect.
- Operational Trajectory A vs. B definition for retrospective cohort application.

Gaps closed (20260424)

- Kantarcioglu full bibliographic confirmation — Mycopathologia 2016, 181(1-2):1-7, PMID 26442855, DOI 10.1007/s11046-015-9949-3.
- Sandler vancomycin trial full integration — all regressive-onset; significant improvement (P=.003); 2-week post-discontinuation deterioration; absent Peptostreptococcus species in all tested fecal samples vs. 93% in adult controls; explicit microbiome-mechanism framing by authors in 2000.
- NCT00936182 structure — three sites (Tarzana/Melbourne/Austin), three PIs (Granpeesheh/Rossignol/Jepson), 2009 registration, seventeen-year silence. Trial design was rigorous: double-blind, randomized, placebo-controlled, pyrosequencing-positive-yeast enrollment, pre-specified behavioral outcome hypothesis. Registered nine years after Sandler framed the hypothesis.
- NCT00936182 results recovery — acknowledged as unrecoverable; the silence is the finding for Clear Evidence companion paper.
- Trajectory A clinical validation — Sandler et al. (2000) documented regressive-onset autism responsive to vancomycin with ecological signature (absent Peptostreptococcus) and post-discontinuation relapse.
- Trajectory A preclinical validation — Qiao et al. (2026) directly demonstrates host-susceptibility-plus-activation-event architecture in Shank3+/- mice with LPS challenge; anti-inflammatory rescue; microglia-TLR4-synapse-engulfment pathway. Authors explicitly frame as preclinical regression model.
- Shank3 distributed-circuit architecture — three papers (Gao 2025 hippocampus; Wu S. 2024 hypothalamic AgRP; Wang 2017 striatopallidal) together document that different Shank3-ASD symptoms localize to different vulnerable circuits, each framework-accessible.

Status

Maturity upgraded 20260424 on strength of Sandler 2000 full integration, Qiao 2026 Trajectory A preclinical validation, and full SHANK3-circuit literature integration (Gao 2025; Wu S. 2024; Wang 2017; Kantarcioglu 2016). Three deployment paths now available:

- SHANK3-subtyped Architect Report — ready-to-draft. Narrower scope centered on SHANK3-associated ASD with direct preclinical validation; addresses the ~40% regression rate with specific mechanism claims.
- Clear Evidence No Trial #2 companion (NCT00936182) — ready-to-draft. Stands independent of framework commitment. Three-site rigorous RCT registered 2009, seventeen years silent. Registered nine years after Sandler framed the hypothesis. The artifact is the silence.
- Full-spectrum Autism Architect Report — ready-to-draft. Sandler 2000 clinical validation plus Qiao 2026 preclinical validation now supply the Trajectory A backbone; the remaining gaps (MRI stratification, maternal antibiotic timing, pediatric mycobiome normative data, operational Trajectory A/B definition) can be addressed in the paper itself or flagged as future work rather than gating publication.

Seed 018: Chronic Insufficient Venous Return as Symbiont-Managed Capacitance Phenotype [Series: AS]

Template: A (Condition) **Maturity:** developing **Last revised:** 20260425 **Publication target:** Stuck State series entry as full Architect Report; Clear Evidence No Trial companion candidate (antifungal trial in hyperadrenergic POTS subset).

Claim (one sentence)

Chronic insufficient venous return, expressed clinically as hyperadrenergic postural orthostatic tachycardia syndrome, splanchnic pooling phenotypes, chronic venous insufficiency, and inferior vena cava syndrome variants, represents a stuck state in which *C. albicans*-directed management of venous capacitance, electrolyte conservation, and adrenergic tone has decoupled from the host's standard volume regulation, producing the configuration mainstream cardiology cannot mechanistically reconcile: hypovolemia with inappropriately low renin, low aldosterone, splanchnic blood pooling, and elevated standing norepinephrine.

What this seed is NOT

This seed is not a review of POTS, chronic venous insufficiency, or IVC syndrome literature. It is not a clinical practice guideline. It is not a claim that all chronic insufficient venous return is symbiont-mediated. It is not a treatment protocol. It is a framework paper proposing that the configuration of insufficient venous return paired with inappropriately low renin-aldosterone activity and elevated sympathetic tone is the diagnostic signature of disrupted symbiont governance at the splanchnic capacitance reservoir, and that the subset displaying this configuration is the testable target population for antifungal intervention.

Framework basis

- (Craddock, Biochemical Computer) — ECS-mediated governance of pre-synaptic norepinephrine release at sympathetic terminals; muscarinic-like cholinergic receptor for parasympathetic input; symbiont as conductor of host autonomic tone.
- (Craddock, Saline Oscillation) — Section 4.3 vascular mechanics: cardiac suction, IVC dynamics, reversed renal pressure differential, ECS-mediated selective perfusion management as a unified architecture; saline oscillation as the upstream electrolyte cycle this system serves.
- (Craddock, Longitudinal Case Study) — IVC narrowing as central post-1995 anatomical signature documented across 27 years of imaging; 1969–2022 staging of progressive disengagement.
- (Craddock, Stuck-State Umbrella) — stuck program mode model; this seed extends the model into cardiovascular autonomic regulation.
- (Craddock, Pan-Mammalian) — coevolutionary positioning of mesenteric venous bed as symbiont's territorial home and the splanchnic reservoir as managed substrate buffer.
- 2018 Transition Case Study — laboratory documentation of the hyperadrenergic-with-low-renin configuration as the framework's predicted phenotype during acute disengagement.

Conventional understanding and its gaps

Mainstream physiology recognizes insufficient venous return as a final common pathway with multiple proximate causes: hypovolemia, excessive venous capacitance, impaired sympathetic venoconstriction, mechanical obstruction, and cardiac filling failure. POTS classification carves the phenotype into neuropathic, hyperadrenergic, hypovolemic, and deconditioning subtypes, with explicit acknowledgment that subtypes overlap and that no unified mechanism explains the phenotype.

The configuration that mainstream cannot reconcile is the patient who is volume-deficient with inappropriately low plasma renin activity, low aldosterone, and elevated standing norepinephrine. Renin-angiotensin-aldosterone is supposed to engage in hypovolemia. When it does not, the literature flags the finding and moves on. No proposed mechanism explains why the conservation arm of volume regulation would be silent in a patient whose sympathetic compensation is fully engaged. The norepinephrine transporter loss-of-function explanation for hyperadrenergic POTS, increasingly recognized as epigenetic rather than genetic, has no causal model attached to it.

The framework reads this configuration as a signature: the symbiont is sequestering electrolyte and managing volume according to its own setpoint, and the host's renin-aldosterone arm is correctly registering that setpoint as "filled" while the standard sympathetic arm reads peripheral effective volume as low and compensates. The two arms do not contradict; they are answering different questions.

Mechanism (framework reading)

The splanchnic venous bed holds 25–30% of total circulating blood volume and is the dominant sympathetically-modulated reservoir in the mammalian body. Mesenteric veins are approximately 30 times more sensitive to norepinephrine than mesenteric arteries, with α1-adrenergic receptors predominant and α2-adrenergic receptors contributory. The asymmetry is not coincidental. The vascular bed in which the symbiont resides is also the bed most finely tuned to adrenergic control, providing the symbiont with a high-gain control point over the largest single blood volume reservoir in the body.

ECS-mediated pre-synaptic CB1 modulation of norepinephrine release at these terminals (Paper A catecholamine section) gives the symbiont indirect governance of splanchnic venoconstriction without requiring direct catecholamine sensing. Wurster et al. (2021) confirmed *C. albicans* does not respond to physiologic catecholamines in vitro, consistent with the symbiont being upstream of the adrenergic cascade rather than a downstream listener. The faucet, not the gauge.

When ECS governance is intact, the splanchnic reservoir is held at the symbiont's preferred capacitance, the renin-aldosterone arm calibrates to that managed volume, and host-perceived volume status is stable. When governance is disrupted, by acute organism stress, antifungal exposure, mechanical perturbation, or staged disengagement, the reservoir's capacitance becomes inadequately managed. Blood pools in the splanchnic bed without adrenergic restraint. Effective central volume drops. Baroreflex engages sympathetic compensation through the standard pathway, producing the elevated standing norepinephrine signature, while the renin-aldosterone arm continues to read the symbiont's electrolyte setpoint and remains inappropriately quiescent. The patient presents as hyperadrenergic, hypovolemic, and renin-suppressed simultaneously.

The cerebral venous outflow phenotype documented by Fargen et al. (2025) extends the same logic upward. Glymphatic clearance and cerebral venous drainage are functions the symbiont must manage because the symbiont must manage what is cleared from the central nervous system. Cerebral venous outflow insufficiency under this reading is the cranial expression of the same stuck-state architecture that produces splanchnic pooling below.

The structural IVC narrowing documented in (Craddock, Longitudinal Case Study) is not a separate pathology but the long-arc anatomical signature of decades of managed venous return, in which the symbiont uses partial IVC compression to reverse the renal pressure differential and preserve cerebral

perfusion through the unobstructed superior vena cava path. The hyperadrenergic POTS phenotype is the early-stage expression of the same governance pattern, observable before structural remodeling completes.

Predictions (numbered, with evidence class)

1. **Hyperadrenergic POTS patients with low plasma renin and low aldosterone display elevated stool *C. albicans* burden compared to POTS patients without the renin-suppressed signature.** [Cross-sectional observational; testable with existing biobank samples.]
2. **Antifungal intervention in the hyperadrenergic POTS / low-renin subset produces measurable improvement in standing norepinephrine, orthostatic tachycardia magnitude, and patient-reported orthostatic intolerance within 6–12 weeks.** [Pre-registered Clear Evidence No Trial protocol candidate.]
3. **Norepinephrine transporter (SLC6A2) methylation status correlates with mycobiome composition in hyperadrenergic POTS, and antifungal intervention produces detectable methylation change at the locus.** [Epigenetic mechanism validation; longitudinal sampling required.]
4. **Splanchnic blood pool volume measured by impedance plethysmography correlates with mycobiome load across POTS subtypes, with the strongest correlation in the hyperadrenergic-with-low-renin subset.** [Cross-sectional physiology; non-invasive.]
5. **Cerebral venous outflow insufficiency phenotypes show elevated mycobiome markers compared to matched controls without cerebral venous symptoms.** [Cross-sectional, links to Fargen 2025 patient population.]
6. **Pediatric onset of insufficient venous return phenotypes (POTS, orthostatic intolerance) follows perturbation events (antibiotic course, viral infection, surgical anesthesia) at higher frequency than expected by chance, paralleling the perturbation-triggered trajectory in Seed 017.** [Retrospective chart review; testable in existing pediatric POTS cohorts.]

Existing literature support

- Wurster, S. et al. (2021). *Pharmacological serum concentrations of epinephrine and norepinephrine do not affect growth rate, morphogenesis, stress tolerance, and virulence of Candida albicans*. Medical Mycology, 59(1), 102–105.
- Fargen, K.M. et al. (2025). *Cerebral venous outflow revisited: Contemporary insights to simplify a complex disease*. Interventional Neuroradiology.
- Stewart, J.M. et al. (2002). *Pooling in chronic orthostatic intolerance*. Circulation.
- Garland, E.M. et al. (multiple). Hyperadrenergic POTS with low plasma renin and aldosterone configuration documentation.
- Bayles, R. et al. (2012). *Epigenetic modification of the norepinephrine transporter gene in postural tachycardia syndrome*. Arteriosclerosis, Thrombosis, and Vascular Biology, 32(8), 1910–1916.
- Schlicker, E. & Kathmann, M. (2001). Modulation of transmitter release via presynaptic cannabinoid receptors. Trends in Pharmacological Sciences.

- Lyte, M. (multiple). Microbial endocrinology literature on bacterial response to host catecholamines.
- Fedorowski, A. et al. (2024). *Gut microbiota composition is altered in postural orthostatic tachycardia syndrome and post-acute COVID-19 syndrome*. Scientific Reports.
- Botschuijver et al. (2017). Mesentery as fungal-dysbiosis-responsive territory; antifungal reversal of visceral hypersensitivity in rat model.

Counter-arguments to address

Counter: POTS is fully explained by hEDS connective tissue laxity, deconditioning, and autonomic neuropathy, none of which require symbiont involvement. **Response:** The framework does not displace these explanations for the cases they cover. It addresses the subset of patients whose configuration (low renin with low aldosterone with elevated standing norepinephrine and splanchnic pooling) is unexplained by hEDS, deconditioning, or neuropathy. The prediction is that this subset is mycobiome-distinguishable and antifungal-responsive; the test is empirical.

Counter: Wurster et al. (2021) showed *C. albicans* does not respond to catecholamines, which means the organism is unrelated to the catecholamine pathway entirely. **Response:** The Wurster result is consistent with the framework's prediction that the symbiont governs the catecholamine pathway upstream rather than responding to it downstream. The negative result establishes only that *C. albicans* is not a catecholamine-target; it is silent on whether *C. albicans* is a catecholamine-modulator. The CB1 pre-synaptic mechanism is the proposed modulation pathway and is independent of direct catecholamine sensing.

Counter: The female predominance of POTS (4–5:1) suggests sex-linked or hormonal mechanisms unrelated to fungal colonization. **Response:** Estrogen and progesterone are documented modulators of *C. albicans* virulence and biofilm formation (Zhang et al., 2000; subsequent literature). The female predominance is consistent with rather than counter to the framework. The seed should engage this directly rather than leave it implicit.

Counter: Inappropriately low renin in hypovolemia is a rare laboratory curiosity rather than a diagnostic signature. **Response:** It is rare in the absence of a unifying mechanism because there is no diagnostic category to assign it to. The framework provides the category. The test is whether the configuration, once specifically sought, identifies a coherent patient subset.

Counter: The proposed mechanism is unfalsifiable if every clinical phenotype can be absorbed. **Response:** The framework specifies a testable patient signature (hyperadrenergic + low renin + low aldo + splanchnic pooling) and a testable intervention response (antifungal effect within 6–12 weeks). Prediction failure on either axis falsifies the seed's central claim for the subset.

Related existing Redacted Science work

- (Craddock, Saline Oscillation) §4.3 — vascular mechanics architecture this seed extends from foundational mechanism to clinical phenotype.
- (Craddock, Longitudinal Case Study) — IVC narrowing as long-arc anatomical signature; 2009 Tulsa Run dehydration as thirst-suppression episode within the same regulatory architecture.
- (Craddock, Biochemical Computer) catecholamine section — pre-synaptic ECS modulation mechanism this seed applies to splanchnic venous capacitance specifically.
- (Craddock, Stuck-State Umbrella) — parent paper for the stuck state framing.

- 2018 Transition Case Study — laboratory exemplar of the hyperadrenergic-with-low-renin configuration this seed names as diagnostic signature.
- Seed 017 (Autism Stuck State) — perturbation-triggered trajectory model; pediatric POTS prediction (Prediction 6) draws on the same template.

Notes and observations

The Clear Evidence No Trial companion is unusually clean for this seed because the patient population can be defined precisely (POTS diagnostic criteria plus low-renin / low-aldosterone laboratory signature), the intervention is a single antifungal class with established safety data, and the primary endpoints (standing norepinephrine, orthostatic heart rate increment, patient-reported orthostatic intolerance) are quantitative and well-validated. Botschuijver et al. (2017) provides the rat-model causation precedent in the same anatomical territory (mesentery / splanchnic). The trial absence in the human POTS literature is the same pattern Clear Evidence No Trial #1 documented for IBS.

The Fargen 2025 cerebral venous outflow framing is fresh and undersettled in mainstream neurology. Engaging it now positions the framework ahead of the conventional literature's own consolidation of the phenotype.

The pituitary colonization paper to-do connects directly to this seed through the cerebral venous outflow extension. Drafting order matters: this seed completes the venous capacitance / ECS / sympathetic architecture at the systemic level, providing the foundation the pituitary paper builds on for the cranial-specific case.

Sex distribution should be addressed in the body, not deferred to a future paper. Even if the engagement is brief, leaving the 4–5:1 female predominance unaddressed is a credibility cost the framework does not need to pay.

Status

Developing. Advances to ready-to-draft when:

- Bayles 2012 reference verified end-to-end.
- Garland POTS phenotype reference confirmed and pinned.
- Wurster citation verified against Paper A's existing usage to avoid double-citation conflict in deposit.
- Author decision on whether Cerebral Venous Outflow gets its own subsection or remains an extension paragraph.
- Author decision on whether the Clear Evidence No Trial companion deploys with this paper or as a sequenced follow-up.

End of Seed Table. New seeds append here with the next available three-digit number (018, 019, etc.). Series attribute is mutable; primary key is not.