The Anatomy of Immune-Derived Autism

A systems biology dissection of immune-derived autism with constitutional susceptibility architecture

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Companion document: Restoring the Somatostatin Signal in Immune-Derived Autism: Using IMIG, IVIG, and MSC Therapy as Parallel Pathways to Neuropeptide Cascade Recovery

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Abstract

Background

Autism spectrum disorder (ASD) is diagnosed in approximately 1 in 31 children in the United States [1] and carries a four-to-one male predominance that remains mechanistically unexplained. A significant subgroup presents with concurrent immune dysregulation, gastrointestinal dysfunction, sleep disruption, and metabolic abnormalities suggesting a shared biological origin distinct from primarily genetic or structural ASD subtypes. Decades of single-pathway clinical trials have produced inconsistent results in unselected populations, indicating that the relevant patient subgroup has not been prospectively identified.

Hypothesis

We propose that a mechanistically distinct subgroup — immune-derived autism (IDA) — arises from a converging multi-step biological cascade originating in gut pH dysregulation, progressing through immune activation and metabolic disruption, and converging on the silencing of somatostatin-14 (SST-14) interneurons. SST-14 interneuron silencing disrupts the coordinated release of oxytocin, vasoactive intestinal peptide (VIP), and secretin, producing the social, sensory, sleep, gastrointestinal, cognitive, and motor features of the ASD phenotype cluster. Critically, the cascade propagates only in individuals whose constitutional susceptibility profile places multiple biological tipping points within reach of common environmental insults — a susceptibility architecture that explains why most individuals exposed to the same founding conditions do not develop IDA.

Cascade Summary

Seven converging mechanisms: (1) gut pH elevation disabling pepsin-mediated proline bond cleavage, producing amino acid deficiency and intact opioid peptide fragments; (2) opioid peptides driving CCK-mediated gut SST-28 overactivation and blocking CD26-mediated adenosine clearance; (3) adenosine accumulation rate-limiting the methionine synthase cycle; (4) LPS translocation and cytokine elevation activating IDO1 and diverting tryptophan toward quinolinic acid; (5) NF-κB suppression of CREB and SST-14 gene transcription; (6) convergence of excitotoxic and transcriptional suppression establishing a self-reinforcing biological latch; and (7) downstream neuropeptide cascade disruption producing the observable phenotype cluster.

Constitutional Susceptibility Architecture

The founding conditions are common across the general population. The cascade propagates only in individuals whose constitutional susceptibility profile reduces biological headroom at multiple cascade steps simultaneously. Seven tipping points are identified, each with named genetic, enzymatic, or immunological constitutional factors: reduced parietal cell acid output capacity (ATP4A/ATP4B variants); constitutively reduced DPP-IV/CD26 efficiency (Bashir & Al-Ayadhi 2014 [2]); reduced methionine synthase cycle reserve (MTHFR C677T [3,4], MTR/MTRR variants, folate receptor antibodies [5,6]); impaired specialized pro-resolving mediator (SPM) capacity preventing resolution of innate immune activation (ALOX5/ALOX12/ALOX15 variants [7,8,9] — the most novel and least-evidenced tipping point, currently Level 4 in ASD); KMO variants biasing tryptophan metabolism toward quinolinic acid [10,11]; reduced mitochondrial buffering reserve [12,13]; and HLA class II architecture permitting molecular mimicry-driven autoantibody generation [14].

The Estrogen-cAMP Compensatory Axis

Four linked papers establish the compensatory pathway explaining the four-to-one male-to-female ratio. Montminy et al. (PNAS 1986) [15] identified the cAMP response element (CRE) in the somatostatin gene promoter. Montminy et al. (J Neuroscience 1986) [16] established that cAMP drives somatostatin mRNA accumulation in hypothalamic neurons. Aronica et al. (PNAS 1994) [17] established that estradiol activates membrane adenylyl cyclase nongenomically at physiological concentrations. Qiu et al. (J Neuroscience 2003) [18] characterized the complete Gq-mER → Gαq → PLC → DAG → PKCδ → adenylyl cyclase VII → cAMP → PKA → CREB chain in hypothalamic neurons by single-cell RT-PCR, providing a specific molecular explanation for the sex ratio that does not rely on genetic or diagnostic arguments.

Clinical Implications

IDA is distinguishable from genetic and structural ASD subtypes by a biomarker panel including K:T ratio, cytokine profiles, neuronal autoantibody titers, lactate-to-pyruvate ratio, and red blood cell mineral analysis. This panel extends into a **constitutional susceptibility profile** — a genomic and immunological fingerprint measurable before symptom onset, analogous to polygenic risk scores in psychiatry: not deterministic, but identifying individuals who warrant early monitoring and preventive intervention.

Conclusion

IDA represents a biomarker-definable, mechanistically coherent, and clinically actionable ASD subgroup. The two-layer model — cascade mechanism and constitutional susceptibility — provides the foundation for prospective biomarker-stratified intervention trials and offers a unified explanation for phenotypic heterogeneity, treatment inconsistency, and male predominance.

Introduction: A Convergent Cascade Model with Constitutional Susceptibility Architecture

Autism spectrum disorder does not have a single cause. A mechanistically distinct subgroup — immune-derived autism — has a single convergent mechanistic node through which a wide range of founding conditions produce the same downstream outcome. But the cascade model alone is incomplete. The other half is understanding who is constitutionally unable to buffer the insults that initiate it.

A comprehensive body of independent research has established immune dysfunction as a consistent finding across familial autoimmunity, maternal immune activation, neuroinflammation, and autoantibody generation in ASD subgroups [19] — with autoantibodies

in a subset of children documented to target specifically GABAergic interneurons in the cerebellum and superficial cortical layers [19] — the cell class whose silencing is central to the cascade proposed here. A distinct picture of immune dysfunction has emerged from more than a decade of independent replication, yet no prior work has assembled these findings into a mechanistic cascade linking immune activation to a specific interneuron class and its downstream neuropeptide failure.

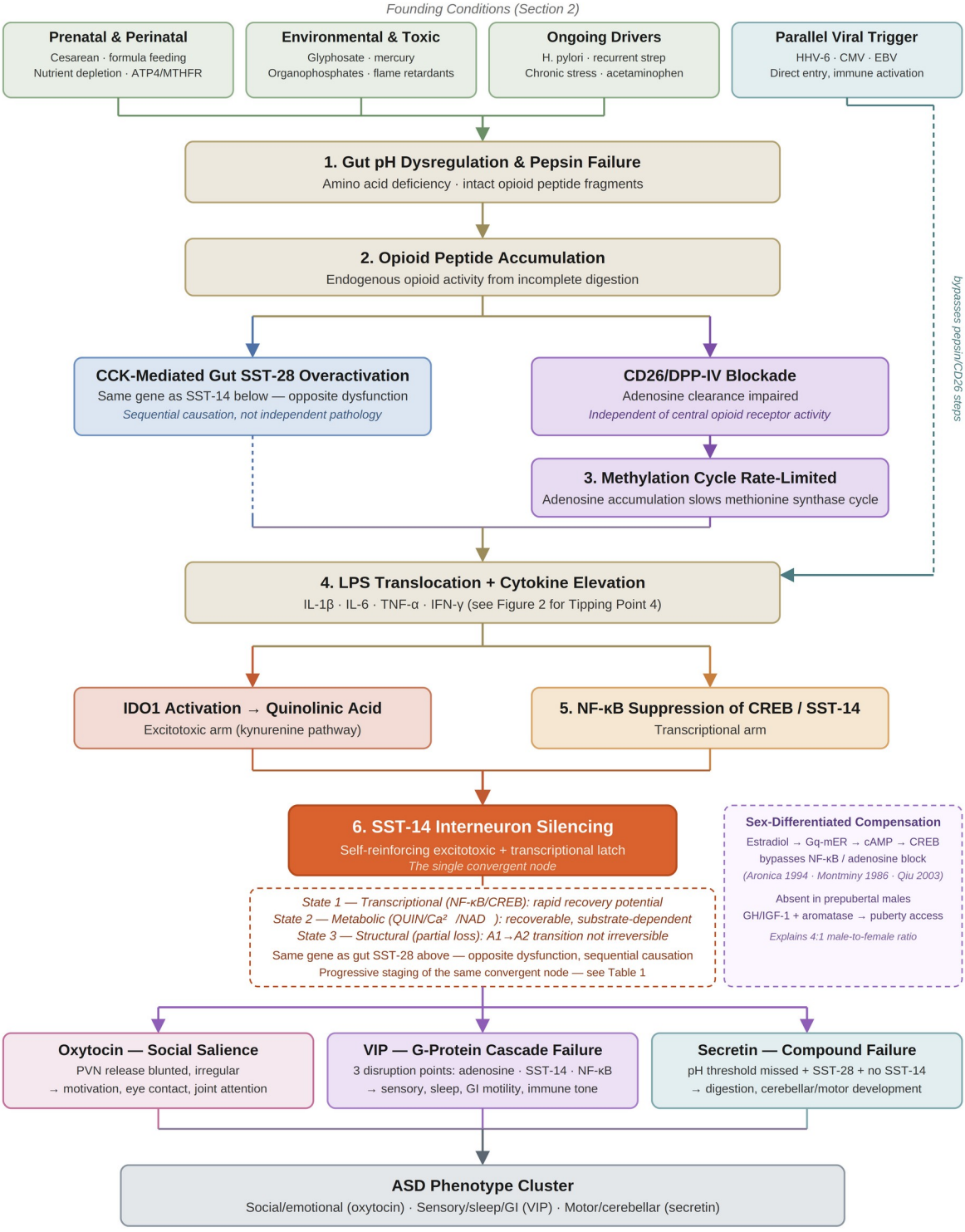
The founding conditions are diverse, and no two children with IDA necessarily share the same combination. Yet a significant proportion share the same outcome because all conditions converge on the same series of intermediate mechanisms and arrive at the same convergent point: SST-14 interneuron silencing in the cortex, hippocampus, and hypothalamus. The apparent heterogeneity of ASD reflects variation in the upstream cascade steps that drove SST-14 silencing — not variation in the downstream mechanism that produced the phenotype.

The founding conditions are common. C-section delivery, formula feeding, antibiotic exposure, acetaminophen use, and glyphosate exposure describe a large fraction of the general pediatric population. Most of those children do not develop IDA. The answer lies in constitutional biology: the genetically and immunologically determined capacity at each cascade step to absorb an environmental load before that step fails. The document is organized in two parts. Sections 2 and 3 describe the environmental founding conditions and then the constitutional susceptibility architecture. Sections 4 through 12 trace the cascade from pepsin failure through SST-14 silencing to the ASD phenotype cluster.

> ***The cascade is not a sequence of independent events. It is a set of simultaneously operating mechanisms converging on a single biological target. And the target is reached only in those whose constitutional susceptibility profile leaves insufficient headroom at enough steps simultaneously.***

Figure 1. The Immune-Derived Autism Cascade: A Convergent Multi-Step Pathway

Founding conditions, seven converging mechanisms, and constitutional staging to SST-14 interneuron silencing



Circled numbers correspond to the seven converging mechanisms in the Cascade Summary (Abstract).
Seven constitutional susceptibility tipping points (Section 3) govern propagation at each stage — see Figure 2 for Tipping Point 4.

Figure 1. The Immune-Derived Autism Cascade: A Convergent Multi-Step Pathway. Founding conditions (Section 2) feed into seven converging mechanisms carrying the cascade from gut pH dysregulation and pepsin failure through the CCK/gut SST-28 and CD26/methylation parallel arms, LPS translocation (with a parallel viral-trigger entry point bypassing the gut-pH route), and the IDO1/NF-κB excitotoxic and transcriptional arms, converging on SST-14 interneuron silencing as the single biological target. The gut SST-28/brain SST-14 polarity (same gene, opposite dysfunction) and the three-state clinical staging model (Section 1) are annotated at the convergent node, alongside the estrogen-cAMP compensatory axis explaining the four-to-one male-to-female ratio. Downstream neuropeptide cascade disruption is shown for each of the three systems individually — oxytocin, VIP, and secretin — with their distinct phenotypic contributions, producing the observable ASD phenotype cluster. Numbered nodes correspond to the seven mechanisms listed in the Cascade Summary (Abstract). See Figure 2 for the constitutional tipping point governing propagation past LPS translocation.

The Three Interneuron States: A Clinical Framework

SST-14 interneuron silencing progresses through three states that reflect the depth of the suppressive burden and determine which interventions are appropriate.

State 1 — transcriptional suppression: the interneuron's structural and metabolic machinery is intact, but SST-14 gene expression is suppressed by NF-κB-mediated CREB inhibition and autoantibody-mediated surface receptor jamming. Removal of the upstream immune burden allows CREB to resume driving SST-14 expression; recovery can be relatively rapid.

State 2 — metabolic exhaustion: chronic quinolinic acid-driven calcium overload and NAD^+ depletion have damaged mitochondrial function. Even when transcriptional suppression is relieved, the interneuron cannot resume tonic firing because mitochondrial substrate is depleted. State 2 requires both immune clearance and metabolic restoration. Constitutional mitochondrial reserve capacity (Tipping Point 6) determines which patients cross into State 2 at a given cascade burden.

State 3 — structural loss: progressive excitotoxic damage has produced partial interneuron loss. The A1/A2 astrocyte reversibility established by Liddelow et al. [20] indicates that even State 3 is reversible. The proposed A1-to-A2 transition mechanism: immunoglobulin therapy reduces IL-1α, TNF-α, and C1q — the three microglial signals necessary and sufficient for A1 polarization — while MSC-derived paracrine factors (TGF-β, HGF, PGE2) actively promote A2 polarization and restore hevin/SPARCL1 synaptogenic protein secretion.

Table 1 summarizes the three-state model.

State	Silencing Mechanism	Key Biomarkers	Primary Intervention	Recovery Trajectory
State 1 Transcriptional suppression	NF-κB-mediated CREB inhibition; autoantibody surface receptor jamming. Interneuron structurally intact.	Elevated K:T ratio; cytokine elevation (IL-6, TNF-α, IL-1β); autoantibody panel positive; homocysteine elevated; normal lactate:pyruvate	IMIG or IVIG to clear immune burden; adjunct protocol (zinc, NAC, sulforaphane, NMN/NR, tributyrin, taurine)	Relatively rapid; weeks to months. Most reversible state.
State 2 Metabolic exhaustion	Mitochondrial failure from chronic quinolinic acid calcium overload and NAD^+ depletion. Gene expression recoverable; energy substrate depleted.	Elevated K:T ratio; elevated lactate:pyruvate; low plasma NAD^+; elevated 8-isoprostane; cytokine elevation; autoantibody panel variable	Immune clearance (IMIG/IVIG) plus metabolic restoration: NAD^+ precursors, mitochondrial support, MSC trophic support	Slower; months. Dependent on mitochondrial restoration alongside immune clearance.

State 3 Structural loss	Partial interneuron loss from sustained excitotoxicity. A1 astrocyte polarization removes trophic and synaptogenic support.	Elevated K:T ratio; low BDNF; reduced hevin/SPARCL1 expression; A1 astrocyte markers elevated; lactate:pyruvate elevated	MSC trophic restoration (IGF-1, BDNF, A2 polarization shift); adjunct protocol sustained; immune clearance to halt further loss	Longest trajectory; months to years. A1/A2 reversibility confirmed [20] but structural recovery partial.

*Table 1. Three-state SST-14 interneuron model. **K:T**, kynurenine-to-tryptophan ratio; IMIG, intramuscular immunoglobulin; IVIG, intravenous immunoglobulin; MSC, mesenchymal stem cell therapy. Biomarker thresholds require prospective validation.*

Founding Conditions: Initiating Insults and Ongoing Drivers of Gut pH Dysregulation

The cascade initiates when the gut environment shifts toward elevated pH, disabling enzymatic systems required for complete protein digestion. Multiple independent conditions can produce this dysregulation and in most affected individuals several operate simultaneously. Each is described below with its specific mechanism of action and forward connection to subsequent cascade steps.

Prenatal and Perinatal Initiating Conditions

Prenatal hormonal or immune disruption during weeks 5–12 of gestation can impair parietal cell development, producing a gut with reduced acid-production capacity from birth. **Cesarean delivery** bypasses maternal microbial seeding; hospital-acquired streptococcal species establish dysbiotic colonization and block CD26 via streptokinase from the first days of life. **Failure to establish nursing** deprives the gut of breast milk oligosaccharides, colostrum immunoglobulins, and motilin-driven motility activation. **Oral contraceptive use** prior to conception depletes B6, B12, folate, zinc, and magnesium; zinc depletion specifically compromises carbonic anhydrase, the enzyme generating hydrogen ions for parietal cell HCl production. **Folate receptor antibodies** block methylfolate transport into the brain independently of dietary status, creating a dual methylation vulnerability from birth. [5,6] **Genetic variants** in proton pump genes, carbonic anhydrase, and zinc transporters narrow the margin within which environmental pressures must operate; MTHFR C677T simultaneously reduces methyl donor availability, compounding adenosine-driven methionine synthase rate-limitation. [3,4]

Environmental and Toxic Initiating Conditions

Glyphosate depletes commensal Lactobacillus, Bifidobacterium, and Enterococcus while sparing LPS-producing gram-negative species, disrupting colonization toward a dysbiotic pH-elevating profile. [21] **Mercury** binds directly to the CD26 receptor site, blocking adenosine deaminase and initiating adenosine accumulation. Prenatal exposure through amalgam, thimerosal, or environmental sources predates any dietary or infectious insult. **Organophosphate pesticides** produce muscarinic receptor downregulation that reduces parietal cell acid responsiveness. Organophosphate flame retardants (TDCIPP, TCPP) saturating infant sleep surfaces until approximately 2015 are detected in cord blood, confirming prenatal neurotoxic exposure. [22,23] **Viral disruption** of adenylyl cyclase signaling — through pertussis toxin ADP-ribosylation of Gαi or herpesvirus G-protein interference — may independently suppress SST-14 transcription through the cAMP-CREB-CRE pathway before the inflammatory cascade is fully established.

Ongoing Drivers That Perpetuate pH Dysregulation

H. pylori alkalinizes the stomach through urease-mediated ammonia production and damages parietal cells directly. **Recurrent streptococcal infections** continuously reintroduce streptokinase, compounding cumulative CD26 blockade burden with each episode. **Chronic sympathetic dominance** suppresses vagal tone and reduces acetylcholine-driven parietal cell acid output — contrary to common belief, chronic stress reduces rather than increases acid production. **Acetaminophen use** depletes glutathione and sulphation capacity in children with already compromised transsulfuration pathways, compounding oxidative stress at the methylation failure step. [21] **Proton pump inhibitor therapy** for reflux that often reflects low motility rather than acid overproduction may deepen the underlying pH dysregulation while relieving the surface symptom. Once CD26 is blocked by any mechanism, the **CD26 self-reinforcing loop** maintains pH elevation independently of the original blocking agent: adenosine accumulation slows the methionine synthase cycle, reducing cellular energy available to drive parietal cell activity.

A Parallel Immune-Activation Input: Chronic and Reactivating Viral Infection

Chronic or reactivated viral infection — human herpesvirus-6 (HHV-6), cytomegalovirus (CMV), and Epstein-Barr virus (EBV) — is a documented independent trigger of glial activation and cytokine elevation (IL-1β, IL-6, TNF-α), the same immune signal that activates IDO1 elsewhere in this cascade. [24] Pro-inflammatory cytokines and interferon signaling are established inducers of IDO1 expression. [25] Unlike the gut-pH-elevating founding conditions described above, this route does not require pepsin inactivation or CD26 blockade to reach IDO1 — it represents a parallel entry point into the immune-activation arm of the cascade rather than an upstream contributor to gut pH dysregulation. A cohort of ASD children with genetic folate cycle deficiency showed markedly elevated rates of active HHV-6 (68%), HHV-7 (72%), and EBV (64%) infection compared to healthy controls. [26] This ASD-specific prevalence finding is correlational; it has not been tested against IDO1 activity or K:T ratio directly and requires prospective validation before being treated as an established cascade input rather than a candidate parallel driver.

> ***The founding conditions are common. The cascade propagates only in those whose constitutional biology leaves insufficient headroom to absorb them. Section 3 describes that constitutional architecture — the filter between insult and cascade.***

Constitutional Susceptibility: Why Only Certain Individuals Cross the Cascade Tipping Points

One of the most important challenges to any multi-insult cascade model is the observation that most individuals exposed to the same founding conditions do not develop the condition. "Threshold dynamics" is a label for an answer, not a mechanistic answer. This section provides the answer by characterizing the constitutional factors that determine where each individual's tipping points sit across the seven cascade steps.

The model is not a single-gene determinism. It is a constitutional susceptibility profile — a combination of genetic, enzymatic, and immunological factors distributed across the cascade that together determine how much environmental load is required before each step fails. The tipping points interact: a child with reduced headroom at three or four steps simultaneously does not need the full complement of founding condition insults to propagate the full cascade. This interaction is analogous to polygenic risk score models in psychiatry — no single variant is deterministic, but the compound burden across variants predicts population-level risk. The

constitutional susceptibility profile proposed here is a prospective instrument awaiting validation, not a demonstrated risk score. Prospective birth cohort studies measuring constitutional susceptibility profiles before symptom onset and tracking cascade propagation represent the required next step.

Tipping Point 1: Gastric Acid Production Capacity

Constitutional factor: reduced baseline parietal cell acid output. ATP4A and ATP4B proton pump gene variants — loss-of-function mutations produce achlorhydria directly [27] — narrow the margin within which H. pylori, PPI therapy, sympathetic dominance, and formula feeding must operate to produce chronic pH elevation above 4.0. CA2 variants reduce hydrogen ion generation; SLC30A zinc transporter variants impair cofactor delivery. The tipping point: constitutional acid production capacity plus all environmental suppressants exceeds the pepsin-activation threshold. Same H. pylori exposure, different constitutional starting point, different outcome.

Tipping Point 2: CD26/DPP-IV Adenosine Clearance Capacity

Constitutional factor: constitutively reduced DPP-IV enzymatic efficiency. Jon Pangborn's clinical laboratory observation that ASD children present with DPP-IV activity substantially below normal is now anchored in the published literature: Bashir & Al-Ayadhi (2014) [2] documented significantly lower plasma DPP-IV activity in ASD children versus controls; EL-Alameey et al. (2018) [28] replicated this finding with casein antibody correlation; Detel et al. (2012) [29] documented reduced DPP-IV activity in inflammatory contexts. Hunter et al. (2003) [30] found no statistically significant deficit but compared ASD children to adults rather than age-matched controls, a methodological limitation noted by Shattock et al. (2004). [31] Vojdani and colleagues [14] demonstrated that the same dietary peptides and xenobiotics that block CD26 also generate anti-CD26 autoantibodies in ASD children, adding a secondary acquired deficit to the constitutional baseline.

This tipping point is mechanistically distinct from the historical opioid excess hypothesis, which proposed behaviorally active opioid peptides crossing the blood-brain barrier. The CD26 mechanism concerns peripheral receptor blockade and adenosine clearance failure at the lymphocyte level — a biochemical mechanism independent of central opioid receptor activation. A child running at constitutively reduced DPP-IV efficiency has no headroom when casomorphin, streptokinase, and mercury simultaneously block remaining capacity. Same blockade load, different constitutional starting point, different cascade outcome.

Tipping Point 3: Methylation Cycle Reserve

Constitutional factor: reduced methionine synthase cycle throughput. MTHFR C677T — documented at elevated frequency in ASD populations [3,4] — reduces methylfolate availability by approximately 70% in homozygous carriers. MTR and MTRR variants reduce methionine synthase activity and reactivation. AHCY variants impair SAH hydrolase. Folate receptor antibodies independently restrict methylfolate delivery to the brain. [5,6] James and colleagues [32,33] documented the methylation metabolic endophenotype directly: ASD children operate at chronically reduced methylation capacity at baseline, with genetic variations in methylation and glutathione pathways correlating with behavioral outcome. The triple bottleneck — MTHFR C677T homozygous plus folate receptor antibodies plus adenosine accumulation — produces methylation failure from three mechanistically independent directions simultaneously. Folate receptor autoantibodies — documented in approximately 75% of one studied ASD cohort [5] and present in parents of ASD children at elevated rates suggesting a familial autoimmune contribution [34] — block methylfolate transport specifically across the blood-brain barrier, creating brain-selective folate deficiency independent of systemic folate status. This makes folinic acid bypass supplementation mechanistically required rather than merely supportive in constitutionally susceptible individuals.

Tipping Point 4: Inflammatory Resolution Capacity

Constitutional factor: impaired capacity to actively terminate innate immune activation. This is the most novel and least-evidenced constitutional tipping point, carrying Level 4 evidence for ASD-specific application and requiring prospective testing. The mechanistic basis is as follows. Normal resolution of LPS-driven innate immune activation requires specialized pro-resolving mediators (SPMs) — lipoxins, resolvins, protectins, maresins — produced from omega-3 PUFA substrates via ALOX5, ALOX12, and ALOX15 lipoxygenase enzymes. ALOX5-deficient and ALOX15-deficient animal models exhibit prolonged inflammatory responses with failure to resolve. [7,8,9] In humans, SPM deficiency characterizes chronic immune disorders. [35,36,37] The proposed model: ALOX5/ALOX12/ALOX15 variants reduce constitutional SPM production capacity, meaning that LPS-driven innate immune activation in constitutionally SPM-impaired children fails to resolve acutely and instead becomes the chronic cytokine state that drives IDO1 and NF-κB activation. TLR4 Asp299Gly and Thr399Ile variants produce dysregulated LPS responses that may compound this failure. [38,39] This is a hypothesis requiring direct testing in ASD populations. Current human ASD evidence is indirect: one pregnancy cohort study noted ALOX5 expression correlating with sensory scores in high-risk infants [40], but no variant association studies in ASD populations have been published. The required validation step is direct measurement of resolvin, protectin, and lipoxin metabolites in stratified ASD cohorts comparing IDA biomarker-positive children to IDA biomarker-negative ASD children and neurotypical controls, combined with ALOX5/ALOX12/ALOX15 genotyping. Until that data exists, Tipping Point 4 remains a mechanistically compelling but empirically unanchored hypothesis. The modifiable component — omega-3 PUFA substrate availability — is nutritionally accessible, but the proposed mechanism is specifically SPM substrate provision for active resolution, not generalized anti-inflammatory suppression.

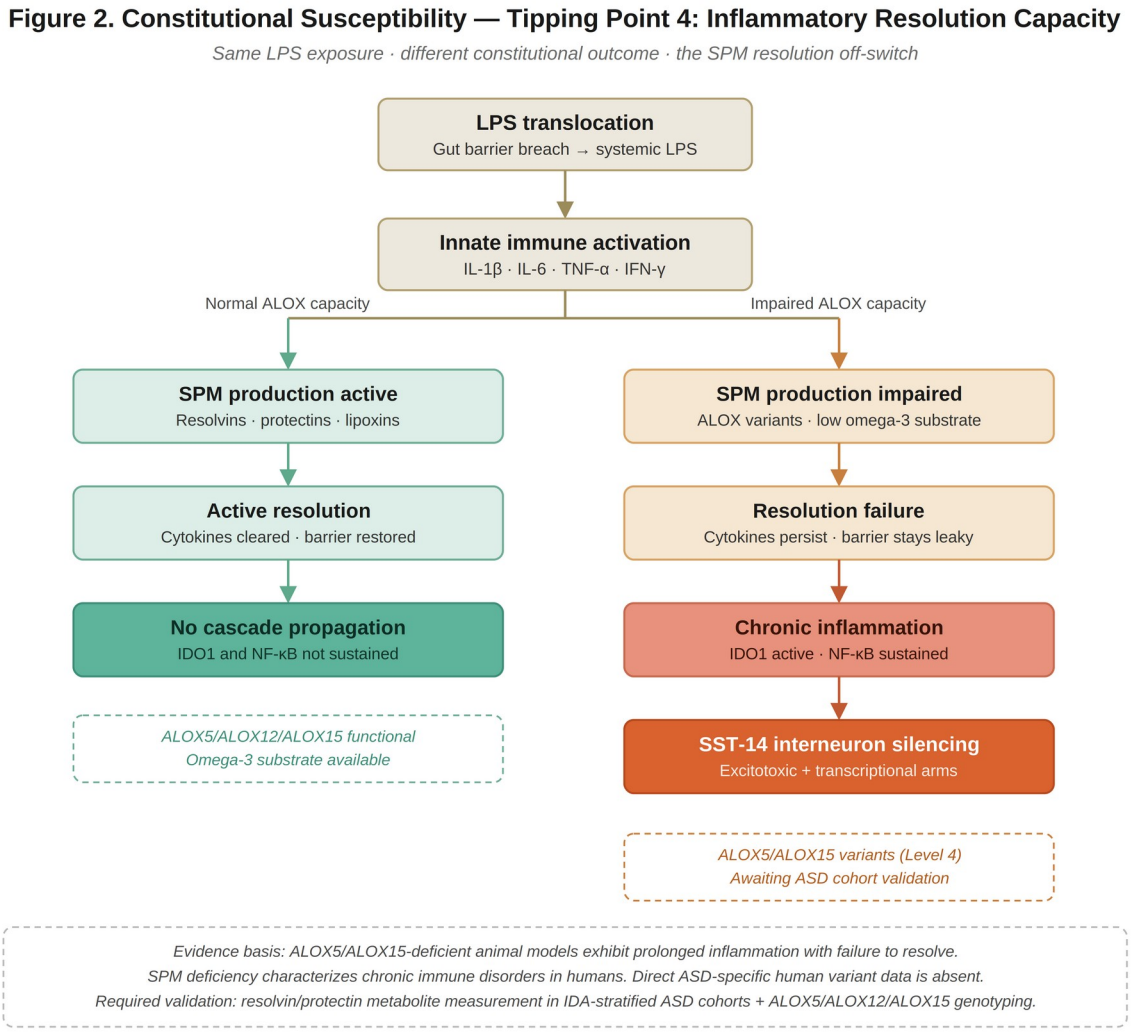


*Figure 2. Constitutional Tipping Point 4: Inflammatory Resolution Capacity. Two parallel pathways show how the same LPS translocation event produces either acute resolution (left, normal ALOX/SPM capacity) or chronic inflammation leading to SST-14 interneuron silencing (right, impaired ALOX/SPM capacity). The constitutional difference is the capacity to produce specialized pro-resolving mediators (SPMs — resolvins, **protectins**, lipoxins) via the ALOX5/ALOX12/ALOX15 lipoxygenase pathway. This tipping point carries Level 4 evidence for ASD-specific application and requires prospective validation. Evidence basis: ALOX-deficient animal models [7,8,9]; SPM deficiency in chronic immune disorders [35,36,37]. Direct ASD human variant data is absent.*

Tipping Point 5: Kynurenine Pathway Excitotoxic Branch Bias

Constitutional factor: KMO (kynurenine 3-monooxygenase) variants determining the constitutional QUIN/KYNA ratio. KMO polymorphisms rs2275163 and rs1053230 have been associated with altered KMO expression and CSF kynurenic acid levels in schizophrenia cohorts, [10,11] establishing that KMO genetic variation produces measurable differences in the QUIN/KYNA ratio in living humans. In ASD, Launay et al. [41] and Bryn et al. [42] document the kynurenine pathway already shifted toward the excitotoxic arm — an elevated QUIN/KYNA

ratio consistent with constitutively high KMO activity, though direct KMO variant data in ASD populations remains to be established. A child with KMO variants favoring QUIN production hits the excitotoxic SST-14 threshold at lower IDO1 activation levels than one with balanced KMO activity.

Tipping Point 6: Mitochondrial Excitotoxic Buffering Reserve

Constitutional factor: mitochondrial reserve capacity and antioxidant genetics. Frye, Rose, and James have documented this directly in ASD: lymphoblastoid cell lines exhibit abnormal mitochondrial reserve capacity and increased vulnerability to oxidative stress challenge before any acute insult is applied. [12] Genetic variations in glutathione pathways (GPX1, GSTM1, SOD2) are documented in ASD cohorts and correlate with behavioral outcomes. [13,32,33] The tipping point determines the State 1/State 2 boundary: children with reduced constitutional reserve cross into metabolic exhaustion at lower quinolinic acid exposure than those with full reserve. Two children with identical upstream cascade burdens can present at different clinical states because their mitochondrial constitutional reserve differs.

Tipping Point 7: HLA-Mediated Autoantibody Susceptibility

Constitutional factor: HLA class II architecture. HLA-DR and HLA-DQ alleles determine which self-mimicking peptides from casomorphin, streptokinase, and mercury-modified self-proteins are presented to CD4+ T cells and therefore which autoantibody responses are generated through molecular mimicry. Vojdani and colleagues [14] demonstrated directly in ASD children that the same dietary peptides and xenobiotics generate different autoantibody profiles in different children. The HLA filter explains why the same streptococcal exposure produces PANS/PANDAS in some children and uncomplicated pharyngitis in others, and why mercury exposure generates CD26 autoantibodies in some ASD children but not neurotypical children with comparable exposure.

Constitutional Susceptibility Profile: Summary Table

Table 2 summarizes all seven tipping points. Evidence levels follow the four-level grading used in the Limitations section. Note that Tipping Point 4 (SPM/inflammatory resolution) is explicitly Level 4 for ASD-specific application and requires prospective validation before clinical application.

Cascade Step	Constitutional Factor	Key Genes / Variants	Mechanism of Reduced Headroom	Interaction with Environmental Load	Evidence Level
1 Gastric acid / pepsin	Reduced baseline parietal cell acid output capacity	ATP4A, ATP4B; carbonic anhydrase II (CA2); SLC30A zinc transporters	Lower constitutive HCl production narrows margin before chronic pH > 4.0; parietal cell autoantibodies add acquired deficit	H. pylori + ATP4A variant crosses threshold that H. pylori alone does not	L2 mechanism; L4 ASD-specific — no direct ASD variant data yet

2 CD26/DPP-IV adenosine clearance	Constitutively reduced DPP-IV enzymatic efficiency [2,28]	DPP-IV functional variants; PREP variants reducing gut peptide pre-clearance	Baseline reduced DPP-IV leaves no reserve; casomorphin + streptokinase + mercury blockade tips system into adenosine accumulation	Normal DPP-IV absorbs opioid peptide load with headroom; constitutionally reduced cannot — same load, different outcome	L2 published DPP-IV reduction in ASD [2,28,29]; L3 compound blockade mechanism [14]
3 Methylation cycle reserve	Reduced methionine synthase cycle throughput; folate receptor antibodies	MTHFR C677T [3,4]; MTR, MTRR; AHCY; folate receptor antibodies [5,6]	MTHFR C677T reduces methylfolate ~70% in homozygous carriers; adenosine-driven inhibition compounds a pre-existing deficit	Triple bottleneck in MTHFR homozygous + folate receptor Ab + adenosine: each individually manageable; together, collapse	L1 methylation endophenotype [32,33]; L2 MTHFR frequency [3,4]
4 Inflammatory resolution capacity	Impaired SPM production; dysregulated TLR4 LPS signaling. Level 4 ASD-specific — requires prospective validation	ALOX5, ALOX12, ALOX15; TLR4 Asp299Gly, Thr399Ile; MUC2, CLDN3, OCLN	ALOX-deficient individuals cannot actively resolve LPS-driven inflammation in animal models [7,8,9]; bridge to human ASD is the highest-novelty, lowest-evidence claim in this document	Requires direct measurement: resolvin/protectin metabolites in stratified ASD cohorts; ALOX variant genotyping in IDA vs. non-IDA ASD	L2 animal models [7,8,9]; L4 ASD-specific — amber shading indicates speculative bridge
5 Kynurenine pathway QUIN/KYNA ratio	Constitutional bias toward excitotoxic (quinolinic acid) branch	KMO rs2275163, rs1053230; IDO1 promoter variants	KMO variants bias kynurenine toward QUIN; same IDO1 activation produces more excitotoxic pressure [10,11]	High-KMO individuals hit excitotoxic SST-14 threshold at lower IDO1 activation level	L1 QUIN/KYNA shift in ASD [41,42]; L2 KMO variants neuropsychiatric [10,11]; L4 ASD-specific
6 Mitochondrial buffering reserve	Reduced mitochondrial reserve capacity and antioxidant	GPX1, GSTM1, SOD2; mtDNA haplogroup	Reduced reserve means lower QUIN exposure crosses into	Constitutional reserve determines State 1/State 2 boundary: same	L1 mitochondrial dysfunction in ASD [12,13,32,33];

	genetic capacity [12,13]	variants; POLG; COQ2/COQ6	State 2 metabolic exhaustion; documented in ASD lymphoblastoid cell lines [12]	cascade burden, different clinical state	L2 reserve capacity as State boundary
7 HLA-mediated autoantibody susceptibility	HLA class II architecture determines molecular mimicry-driven autoantibody generation	HLA-DRB1, HLA-DQ alleles; CTLA4, PTPN22	HLA architecture allows or prevents presentation of casomorphin, streptokinase, mercury-modified self peptides to CD4+ T cells [14]	Same streptococcal exposure produces PANS autoantibodies in susceptible HLA; uncomplicated pharyngitis in others	L2 HLA-II molecular mimicry mechanism; L3 CD26 autoantibodies in ASD [14]; L4 specific HLA alleles

*Table 2. Constitutional susceptibility profile across seven cascade tipping points. L1–L4, evidence levels (see Limitations). Amber-shaded rows (TP1 and TP4) indicate tipping points where the bridge to ASD-specific human data is currently **speculative;** these are the highest-novelty, lowest-evidence claims in this document. QUIN, quinolinic acid; KYNA, kynurenic acid; SPM, specialized pro-resolving mediators; DPP-IV, dipeptidyl peptidase IV.*

The Constitutional susceptibility profile as Predictive Biomarker

The constitutional susceptibility profile extends the diagnostic biomarker panel into a prospective susceptibility screen. A child carrying MTHFR C677T homozygous, reduced plasma DPP-IV activity, folate receptor antibodies, and low plasma omega-3 PUFA levels carries quantifiable susceptibility burden across multiple cascade steps before symptoms appear. This is analogous to polygenic risk score instruments in schizophrenia research — not deterministic, but identifying individuals who warrant early monitoring and preventive intervention. Such a profile warrants early dietary and microbiome protection, omega-3 supplementation to support SPM capacity, avoidance of known CD26 blockers, and monitoring for cascade biomarker elevation. The profile as a clinical instrument requires prospective validation in birth cohort studies before deployment as a screening tool.

The seven tipping points can be operationalized as an additive constitutional burden score: the number of cascade steps at which an individual carries constitutional variants placing them below normal headroom. A child carrying constitutional variants at one or two steps represents a low-burden profile; four or more steps represents a hypothetically high-burden profile for whom the environmental founding conditions pose substantially greater cascade propagation risk. This scoring approach is proposed as a research instrument — analogous to additive polygenic risk scoring in schizophrenia and bipolar disorder research — not as a validated clinical tool. Weighting across the seven tipping points, interaction effects between them, and population-level distribution of scores in ASD versus neurotypical cohorts all require prospective empirical characterization. The IDA trial framework is the appropriate vehicle for that characterization.

How Elevated Gut pH Disables Pepsin and Produces Hidden Malnutrition

Convergent mechanism 1 · upstream of all subsequent cascade steps

Pepsin requires a pH of approximately 2.0 for optimal activity and becomes essentially inactive above pH 4.0. When founding conditions have elevated gastric pH above this threshold, pepsin cannot cleave the proline bonds in casein and gluten proteins. Intact proline-bonded peptide fragments accumulate, resist degradation by small intestinal proteases, and penetrate the intestinal mucosal wall, contributing to the intestinal permeability documented consistently in ASD populations.

Three essential amino acids depend critically on pepsin-mediated proline bond cleavage: phenylalanine, tyrosine, and tryptophan. [43] When pepsin cannot cleave the bonds that contain them, no amount of dietary protein corrects the resulting deficiency. The downstream consequence is **hidden malnutrition** — a child consuming an apparently adequate diet is biochemically deficient in the precursors from which dopamine, norepinephrine, serotonin, and melatonin are synthesized. Low plasma phenylalanine, tyrosine, and tryptophan in the context of adequate dietary protein intake is the diagnostic amino acid panel fingerprint. This establishes the first of two independent tryptophan depletion mechanisms; the second is IDO1-mediated diversion.

Opioid Peptide Accumulation and CCK-Mediated Gut SST-28 Overactivation

Convergent mechanism 2A · gut SST-28 overactivation arm

Casomorphin and gliadorphin — exorphins derived from incompletely digested casein and gluten — bind to mu-opioid receptors and simultaneously block the ADA receptor site on CD26. [14,43] The opioid receptor binding initiates the first of two distinct cascade pathways; CD26 blockade initiates the second. CCK synthesis in response to persistent opioid receptor activation creates a self-reinforcing food preference: opioid receptor activation produces biochemical reward from casein and gluten foods while amino acid deficiency detection systems simultaneously drive protein-seeking toward those same foods, explaining the characteristic food selectivity of affected children as a convergent biological phenomenon rather than a behavioral preference.

Chronic CCK overactivation drives gut SST-28 — the 28-amino-acid intestinal form produced by D-cells — into sustained overexpression. SST-28 suppresses the entire digestive hormone cascade: gastric acid output falls, secretin release is suppressed, VIP-driven gut motility is reduced, and motilin-stimulated peristalsis is impaired.

> ***In the gut, SST-28 is overactive — tonically suppressing the digestive hormone cascade. In the brain, SST-14 is silenced — failing to coordinate the neuropeptide cascade. Same gene, same precursor, opposite dysfunction, sequential causation.***

CD26 Blockade, Adenosine Accumulation, and Methylation Cycle Impairment

Convergent mechanism 2B · methylation failure arm

In parallel with CCK-mediated SST-28 overactivation, casomorphin and gliadorphin initiate a second mechanistically distinct pathway through CD26. This mechanism is independent of central opioid receptor activation: it concerns peripheral blockade of adenosine deaminase at the lymphocyte CD26 receptor, a biochemical mechanism unrelated to the historical opioid excess behavioral hypothesis. Three additional substances block the same receptor site: streptokinase, mercury, and genetic CD26 receptor inefficiency — all demonstrated by Vojdani and colleagues to bind CD26 and induce autoantibodies against it in ASD children. [14] Reduced DPP-IV activity has been independently documented in ASD populations; susceptible individuals appear to

begin with constitutively compromised adenosine clearance that is then further burdened by dietary peptide, bacterial, and xenobiotic blockade. [29]

Adenosine accumulation directly rate-limits methionine synthase, the central enzyme of the methylation cycle that converts homocysteine back to methionine and regenerates SAMe. When methionine synthase activity is rate-limited, SAMe production falls and S-adenosylhomocysteine accumulates. The methylation cycle stalls, producing simultaneous failure of neurotransmitter synthesis, immune cell switching, DNA methylation and gene expression regulation, and cellular energy production. [44]

Elevated plasma homocysteine above 10 μmol/L is the clinical laboratory fingerprint of this mechanism. [32,33] These physical features are well-documented in severe methylation disorders such as classic homocystinuria [45] and may be observed to a lesser degree in milder methylation insufficiency: joint hypermobility, elongated hyperextensible fingers, pectus excavatum, and pale or translucent skin from impaired collagen and elastin synthesis; and low muscle tone with reduced exercise tolerance from creatine synthesis failure — approximately 40% of total SAMe output normally supports creatine synthesis. [46] Adenosine accumulation also activates inhibitory G-protein-coupled adenosine receptors on SST-14 interneurons, suppressing adenylyl cyclase through Gαi and reducing cAMP production independently of NF-κB-mediated CREB suppression. [47]

Intestinal Barrier Disruption, LPS Translocation, and Systemic Immune Activation

Convergent mechanism 3 · primary immune activation input

Penetration of the intestinal mucosal wall by proline-bonded peptides creates a conduit through which lipopolysaccharide (LPS) enters systemic circulation continuously. LPS is one of the most potent known activators of the innate immune system: at nanogram concentrations it initiates production of IL-1β, IL-6, TNF-α, and IFN-γ. Activated microglia produce IL-1α, TNF-α, and complement component C1q — the three signals that drive A1 astrocyte polarization. [20,48] Whether this LPS-driven innate immune activation resolves acutely or becomes chronic is determined by the individual's SPM resolution capacity — the constitutional Tipping Point 4 described above. Chronic LPS-driven cytokine elevation activates IDO1 and NF-κB through the mechanisms described in the following sections.

IDO1 Activation, the Kynurenine Pathway, and Excitotoxic Pressure on SST-14 Interneurons

Convergent mechanism 4A · excitotoxic arm of SST-14 silencing

Sustained cytokine elevation activates IDO1, diverting tryptophan from serotonin synthesis toward kynurenine. Chronic inflammatory environment maintains persistent IDO1 activation, producing a double tryptophan depletion: pepsin inactivation restricts supply from above; IDO1 continuously diverts available tryptophan from below. The K:T ratio above 0.030 is a direct quantitative measure of active IDO1-driven diversion. [41,42,49,50]

The kynurenine pathway bifurcates. The neuroprotective branch produces kynurenic acid (KYNA) through kynurenine aminotransferase. The excitotoxic arm — preferentially activated by the same inflammatory cytokines driving IDO1 — produces quinolinic acid (QUIN) through KMO. The constitutional KMO variant architecture (Tipping Point 5) determines the QUIN/KYNA ratio for a given level of IDO1 activation. [10,11]

QUIN is a potent endogenous NMDA receptor agonist whose overstimulation forces calcium entry into neurons beyond mitochondrial buffering capacity. SST-14 interneurons are

disproportionately vulnerable: their tonic high-frequency firing demands continuous ATP production. The NMDA magnesium block is simultaneously compromised by magnesium depletion from malabsorption and by AMPA receptor disinhibition from reduced SST-14 inhibitory tone — producing calcium overload substantially greater than either mechanism would independently generate. Elevated red blood cell calcium on comprehensive mineral analysis is the measurable correlate. Further along the kynurenine pathway, QUIN converts to NAD^+; under chronic IDO1 activation, NAD^+ consumption by mitochondrial stress response mechanisms exceeds replacement capacity, further compromising SST-14 interneuron tonic firing. [41]

Direct Cytokine-Mediated Suppression of SST-14 Gene Expression via NF-κB and CREB

Convergent mechanism 4B · transcriptional arm of SST-14 silencing

In parallel with the IDO1-kynurenine excitotoxic arm, the same cytokines — IL-1β, IL-6, TNF-α — independently suppress SST-14 gene expression through a transcriptional mechanism that operates entirely separately from excitotoxic calcium overload. Pro-inflammatory cytokines activate NF-κB on SST-14 interneurons; NF-κB suppresses CREB, the transcription factor that drives SST-14 gene expression through the somatostatin gene's cAMP response element. [15] The interneuron's structural machinery remains largely intact — its gene expression has been turned down by the immune environment surrounding it. This is the most clinically reversible form of SST-14 silencing: remove the cytokine load and CREB resumes driving SST-14 expression. This reversibility is the mechanistic basis for the clinical response to immunoglobulin therapy — both IVIG and the lower-cost intramuscular IMIG developed by Dr. Pieter R. Fourie — in State 1 patients.

How CREB Activation Is Blocked: Two Independent Mechanisms Converging on a Single Transcription Factor

To understand why this suppression occurs and why it is so difficult for the cell to overcome, it helps to understand what CREB normally does and what the two cascade mechanisms each take away from it.

What CREB normally does. The somatostatin gene contains a specific 8-base DNA sequence in its promoter region — the cAMP response element (CRE, sequence 5′-TGACGTCA-3′). [15] The CRE is the binding site for CREB. When CREB is activated — specifically, when it is phosphorylated by the enzyme PKA — it binds to the CRE and switches on SST-14 gene transcription. More CREB activation means more SST-14 gene expression means more SST-14 peptide produced. The CRE is not physically blocked or damaged in IDA. The gene is intact. What is disrupted is the signaling machinery that activates CREB in the first place, and the transcriptional machinery that allows active CREB to do its job.

Mechanism A — NF-κB actively hijacks the transcriptional machinery. When pro-inflammatory cytokines activate NF-κB inside the SST-14 interneuron, NF-κB enters the nucleus and competes directly with CREB for two resources. First, it competes for CBP (CREB-binding protein) — the co-activator that both NF-κB and CREB require to drive transcription. Under inflammatory conditions NF-κB wins that competition, leaving CREB without the co-activator it needs even when CREB itself is present and partially phosphorylated. Second, NF-κB recruits histone deacetylases (HDACs) to the chromatin surrounding the somatostatin gene promoter, compacting the chromatin and reducing physical accessibility of the CRE site. The CRE is present, CREB may be present, but the co-activator machinery has been redirected, and the DNA itself has been made less accessible. The transcriptional machinery has been captured by the inflammatory response. [51]

Mechanism B — Adenosine starvation of the cAMP signal. CREB requires phosphorylation by PKA to become active. PKA is activated by cAMP. cAMP is produced by adenylyl cyclase. In IDA,

adenosine accumulation from CD26 blockade activates inhibitory Gi-coupled adenosine receptors on SST-14 interneurons. Those receptors suppress adenylyl cyclase through Gαi. [47] Less adenylyl cyclase activity means less cAMP produced. Less cAMP means less PKA activation. Less PKA activation means CREB is not phosphorylated. Unphosphorylated CREB cannot activate the CRE even if it is bound to the DNA. The ignition exists but the signal that fires it has been cut off upstream. This mechanism operates independently of NF-κB — it is not inflammatory suppression of transcription; it is upstream signal starvation of the activating enzyme.

Mechanism B2 — Mu-opioid receptor: a second independent Gi input. A second Gi-coupled receptor input suppresses adenylyl cyclase simultaneously and independently: casomorphin and gliadorphin bind directly to mu-opioid receptors (MOR) on SST-14 interneurons, activating Gαi through a route entirely distinct from adenosine accumulation. The mu-opioid Gi suppression operates at approximately 52% inhibition of adenylyl cyclase activity (DAMGO EC50 ≈ 37 nM) [52] and is present as long as opioid peptide load persists in circulation — independent of adenosine clearance. The two Gi inputs operate additively: adenosine clearance support alone is therefore insufficient to fully restore cAMP output while opioid peptide load from gut pH dysregulation persists. Removal of both inputs simultaneously — through gut pH correction reducing casomorphin production and immune clearance reducing the inflammatory adenosine cascade — is required for full adenylyl cyclase responsiveness. Forskolin, by activating adenylyl cyclase directly at the catalytic subunit, bypasses both Gi inputs simultaneously regardless of receptor occupancy. [53]

Why both mechanisms operating simultaneously is worse than either alone. Mechanism A suppresses CREB even when cAMP is present. Mechanism B prevents cAMP from activating CREB in the first place. Together they attack the same transcription factor from two independent directions: one removes the co-activator and closes the chromatin; the other prevents the phosphorylation signal from arriving. A cell facing only Mechanism A could partially compensate by increasing cAMP production — enough phosphorylated CREB might outcompete NF-κB for CBP. A cell facing only Mechanism B could partially compensate if the inflammatory environment were mild enough that NF-κB-CBP competition were incomplete. Both operating simultaneously removes both compensatory routes. SST-14 gene expression is suppressed from above and below simultaneously.

Where the estrogen compensatory axis fits. The Gq-mER estrogen pathway characterized by Qiu et al. [18] generates cAMP through an entirely different route: Gq-mER → Gαq → PLC → DAG → PKCδ → adenylyl cyclase VII → cAMP. This pathway does not go through the Gs-coupled receptor that adenosine suppresses via Gαi. It bypasses Mechanism B. In females, estradiol can therefore drive cAMP production and CREB phosphorylation even when adenosine has suppressed the conventional cAMP route. It does not bypass Mechanism A — NF-κB is still competing for CBP — but it partially compensates for Mechanism B. A female carrying equivalent IDA cascade burden retains some CREB phosphorylation capacity through this bypass that a prepubertal male cannot access. The CRE gets partially activated. SST-14 gene expression is reduced but not fully silenced. That partial residual expression is enough to provide meaningful functional protection. At puberty, testosterone-to-estradiol conversion via brain aromatase gives males their first access to this bypass — the mechanistic basis for the partial spontaneous improvement families sometimes observe in adolescent males with IDA.

Autoantibody-Mediated Functional Silencing

Simultaneously with transcriptional suppression, the adaptive immune system produces autoantibodies against neural surface proteins on SST-14 interneurons, impairing membrane signal transduction independently of transcriptional suppression. [14] Transcriptional suppression reduces SST-14 production at the gene expression level; autoantibody binding impairs the functional output of whatever SST-14 signaling remains. The HLA architecture (Tipping Point 7) determines which individuals generate these autoantibodies from the same antigenic exposure.

Convergence on SST-14 Interneuron Silencing and the Self-Reinforcing Biological Latch

Convergent mechanism 5 · the mechanistic node

The IDO1-kynurenine excitotoxic arm and the NF-κB-CREB transcriptional suppression arm arrive at the same cellular target simultaneously, along with adenosine-mediated cAMP suppression and autoantibody-mediated functional jamming. SST-14 interneurons are suppressed at four independent levels simultaneously: metabolic depletion from quinolinic acid excitotoxicity; transcriptional suppression via NF-κB; reduced cAMP activation of CREB via adenosine; and surface receptor jamming via autoantibodies.

SST-14 interneurons maintain tonic high-frequency firing, demanding continuous mitochondrial ATP. When quinolinic acid-driven calcium overload damages mitochondrial function and NAD^+ depletion removes the energy cofactor simultaneously, these high-demand cells face an energy crisis. The transition from transcriptionally suppressed but metabolically intact (State 1) to metabolically exhausted (State 2) is determined by constitutional mitochondrial reserve capacity (Tipping Point 6). Microglial activation produces IL-1α, TNF-α, and C1q — driving A1 astrocyte polarization. A1 reactive astrocytes suppress synaptogenesis, reduce BDNF production, withdraw hevin and SPARCL1, and impair glutamate clearance. Liddelow et al. [20] established that the A1 reactive state, once formed, does not spontaneously revert simply because the inducing microglial signals are withdrawn — but that it can be actively reverted by specific counter-signals such as TGF-β, demonstrating the state is a modifiable functional program rather than a fixed structural change, directly challenging the assumption that the adult brain's plasticity window is irreversibly closed.

SST-14 silencing removes the anti-inflammatory inhibitory tone that SST-14 interneurons normally exert on microglia and reactive astrocytes. When SST-14 output falls, microglial reactivity increases, cytokine levels rise, IDO1 activity increases, quinolinic acid production increases, and excitotoxic pressure on remaining SST-14 interneurons intensifies. The system cannot self-correct because the mechanism that should initiate correction has been disabled. This is the biological latch that explains why IDA tends to persist and deepen rather than spontaneously resolving, and why partial interventions addressing single cascade components produce transient improvement followed by relapse. We propose that IMIG will resolve the source of the inflammation upstream, allowing the downstream mechanisms such as SST-14 interneuron activity to regain function.

Neuropeptide Cascade Disruption: Oxytocin, VIP, and Secretin

Convergent mechanism 6 · downstream of the node

When SST-14 activity falls below functional threshold, three neuropeptide systems lose their upstream coordinating signal simultaneously. [54]

Oxytocin: Loss of Coordinated Social Salience Signaling

SST-14 interneurons in the paraventricular nucleus modulate the timing and amplitude of oxytocin release. When SST-14 output is suppressed, oxytocin release becomes blunted, irregular, and uncoupled from social context — a motivational deficit at the neurochemical level rather than a cognitive or structural one. This framing explains the consistent failure of exogenous oxytocin: an early positive signal [55] was followed by the definitive null result of the SOARS-B trial [56] (n=290) and confirmed by systematic review. [57] Exogenous oxytocin cannot restore the circuit timing and social-contextual coupling that SST-14 interneuron coordination provides.

A second, mechanistically independent route to oxytocin suppression operates through IDO1 directly, without requiring SST-14 silencing as an intermediate step. Sustained IDO1 activation diverts tryptophan away from serotonin synthesis; the resulting serotonin deficit impairs 5-HT2 receptor-mediated signaling in the hypothalamic paraventricular nucleus, independently suppressing oxytocin release. Launay et al. [41] directly measured IDO activation, kynurenine pathway metabolites, NAD+ levels, and plasma oxytocin in the same ASD cohort (n=271) and found NAD+ deficit strongly correlated with plasma oxytocin — human evidence for this hypothalamic route as a measured consequence of kynurenine pathway dysregulation, not merely a theoretical one. This second route means oxytocin suppression can occur, or worsen, independent of SST-14 status, reinforcing why oxytocin replacement fails regardless of which upstream mechanism dominates in a given individual.

VIP: G-Protein Cascade Failure Across Four Biological Systems

VIP signaling operates through receptor → Gαs → adenylyl cyclase → cAMP → PKA → CREB. This chain has been disrupted at three independent points simultaneously by the preceding cascade mechanisms: adenosine accumulation activates Gi-coupled adenosine receptors suppressing adenylyl cyclase; SST-14 silencing removes coordinating inhibitory tone; and NF-κB directly suppresses CREB. VIP signaling fails not because VIP is absent but because the intracellular cascade through which it acts has been disrupted at three independent points. The four systems simultaneously affected: suprachiasmatic nucleus circadian synchronization producing fragmented arrhythmic sleep; cortical gain control producing modality-nonspecific sensory processing abnormalities; enteric smooth muscle relaxation producing constipation and delayed transit; and immune anti-inflammatory suppression. [58,59,60]

The Estrogen-cAMP-CREB-SST14 Compensatory Axis and the Male-to-Female Ratio

Montminy et al. (J Neuroscience 1986) [16] established that cAMP drives somatostatin mRNA accumulation in hypothalamic neurons. Montminy et al. (PNAS 1986) [15] identified the 8-base palindrome CRE (5′-TGACGTCA-3′) in the somatostatin gene promoter. Aronica et al. (PNAS 1994) [17] established that estradiol activates membrane adenylyl cyclase nongenomically at physiological concentrations (half-maximal at 10 pM). Qiu et al. (J Neuroscience 2003) [18] characterized the complete intermediate chain in hypothalamic neurons: Gq-mER → Gαq → PLC → DAG → PKCδ → adenylyl cyclase VII → cAMP → PKA → CREB phosphorylation, confirmed by single-cell RT-PCR. Roepke, Ronnekleiv, and Kelly (2011) [61] provide the physiological review of this Gq-mER pathway. The estradiol-generated cAMP partially counteracts NF-κB-mediated CREB suppression in females, providing SST-14 expression that a prepubertal male cannot access — a specific and testable molecular explanation for the four-to-one sex ratio. At puberty, testosterone-to-estradiol conversion via brain aromatase gives males their first access to this pathway, consistent with partial spontaneous improvement in social function observed in some adolescent males.

Secretin: Compound Failure from Above and Below

Secretin faces disruption from two independent directions: gut pH dysregulation prevents duodenal chyme from reaching the pH 4.2 threshold required for S-cell secretin release; gut SST-28 overactivation provides a second suppressive layer. From above, SST-14 silencing removes central neural coordination of gut-brain peptide integration. The secretin trial history illustrates this compound failure and provides early proof-of-concept that recovery is possible. Horvath and colleagues reported behavioral improvements in three autistic children receiving secretin intravenously during a diagnostic procedure [62] — a genuinely secretin-deficient population receiving the deficient molecule via a route that bypasses the blocked S-cell pH-dependent release mechanism. The subsequent controlled literature [63,64] confirmed no consistent benefit in unselected populations, not because the mechanism is wrong but because unselected enrollment diluted the responsive subgroup to statistical insignificance. Secretin receptor expression in the

cerebellum provides a specific mechanistic account for motor coordination difficulties, toe walking, and impaired procedural learning in ASD.

Thalamic Gating Failure: A Second Mechanism for Sensory Dysregulation

SST-14 interneuron silencing in the thalamic reticular nucleus (TRN) holds the thalamic gate continuously open. Sensory signals that should be attenuated at the thalamic relay level arrive at primary sensory cortex with full amplitude, encountering cortical networks that have simultaneously lost VIP-driven dynamic gain control. This two-level filtering failure — thalamic gating disruption and cortical gain control disruption in series — explains both the severity and modality-nonspecific nature of sensory processing abnormalities in ASD. [65]

The ASD Phenotype Cluster: Observable Expressions of Upstream Cascade Failure

Convergent mechanism 7 · observable expression

The clinical features of IDA are simultaneous downstream expressions of a unified upstream mechanism. They are not a collection of independently caused characteristics.

Social motivation and emotional regulation reflect oxytocin pathway loss: reduced social initiation, atypical eye contact, reduced joint attention, and impaired emotional regulation reflect motivational architecture failure rather than structural inability to engage socially.

Sensory processing, sleep architecture, and gut motility reflect VIP pathway loss across four systems simultaneously: sleep disruption (affecting 40–80% of autistic individuals) from circadian oscillator desynchronization; modality-nonspecific sensory abnormalities from the two-level thalamic-cortical filtering failure; gastrointestinal motility disturbance; and immune dysregulation. These four domains converging in the same child are the predictable simultaneous consequence of losing a single neuropeptide whose functional territory spans all four systems.

Digestive function, cerebellar development, and gut-brain metabolism reflect secretin pathway loss: digestive enzyme insufficiency compounding initial nutritional deficiency; and motor coordination difficulties, toe walking, and impaired procedural learning from cerebellar peptide signaling failure.

Cognitive rigidity and impaired neural plasticity reflect A1 astrocyte polarization: reduced synaptogenesis, BDNF deficiency, and withdrawal of hevin/SPARCL1-mediated thalamocortical connectivity. As established by Liddelow et al., [20] the A1 polarization state does not passively reverse when the microglial signaling that maintains it is withdrawn, but can be actively reverted by specific counter-signals (for example TGF-β) — directly challenging the assumption that neural plasticity windows close irreversibly in early childhood, while underscoring that recovery requires active intervention rather than passive resolution.

Synthesis: The Two-Layer Model, Clinical Implications, and Testable Predictions

Integration and clinical translation

The Two-Layer Model for Immune-Derived Autism

This document presents a two-layer model. The first layer — the convergent cascade — describes what goes wrong: seven simultaneously operating biological mechanisms converging on SST-14

interneuron silencing and the downstream neuropeptide cascade disruption producing the ASD phenotype cluster. The second layer — constitutional susceptibility — describes who it goes wrong in: the genetic and immunological profile determining whether the same environmental insults propagate into a full cascade or are absorbed without consequence.

The cascade is convergent: any combination of founding conditions can initiate it at sufficient burden, explaining why IDA appears etiologically heterogeneous while remaining mechanistically consistent at the convergent node. The cascade is self-reinforcing: the biological latch explains persistence and treatment resistance. The cascade is sex-differentiated: the estrogen-cAMP-CREB-SST14 compensatory axis provides a specific molecular explanation for the four-to-one sex ratio. The cascade is constitutionally gated: the susceptibility profile determines who enters it. The downstream biomarker signature identifies IDA retrospectively; the constitutional profile identifies susceptibility prospectively.

Why Prior Clinical Trials Failed to Demonstrate Benefit

Exogenous oxytocin addresses one downstream neuropeptide output without restoring upstream coordinating architecture. Secretin addresses one downstream deficiency without resolving the compound upstream failure. Immunoglobulin trials enrolled children whose ASD arises from genetic, structural, or non-immune mechanisms alongside the IDA subgroup, diluting the biological response to statistical insignificance. The Frye et al. folinic acid series [5,6,66] represents the single published intervention producing consistent positive results, following directly from the principle this document establishes: prospective biomarker stratification — folate receptor antibody positivity — isolates the treatment response from the noise of unselected enrollment.

Regressive Autism and PANS/PANDAS

Regressive autism — skill loss between 18 and 36 months after apparently normal early development — is not a distinct subtype but a temporal expression of the same cascade under threshold dynamics. Compensatory mechanisms, including the estrogen-cAMP-CREB-SST14 pathway in females, may maintain adequate SST-14 output while cascade burden accumulates. A second biological challenge — febrile illness, antibiotic-induced microbiome disruption, or streptococcal infection producing acute IDO1 activation — crosses the threshold at which SST-14 interneurons can no longer maintain coordinating output. The regression is the moment the threshold was crossed, not the moment pathology began. PANS and PANDAS represent the accelerated acute expression of the same cascade: streptococcal molecular mimicry drives rapid autoantibody production against SST-14 interneuron surface proteins, producing sudden-onset neuropsychiatric presentation. The HLA architecture (Tipping Point 7) determines which children generate these autoantibodies from the same streptococcal exposure. [67]

ADHD and AuDHD as Regional Variants of SST-14 Silencing

The cascade mechanism produces ADHD-relevant features through phenylalanine and tyrosine deficiency depleting dopaminergic precursors, SAMe depletion impairing COMT-mediated catecholamine regulation, and prefrontal SST-14 silencing reducing executive function inhibitory tone. The clinical distinction between ASD and ADHD may reflect the regional distribution of SST-14 silencing: predominant prefrontal silencing produces ADHD-predominant features; predominant hypothalamic, amygdala, and sensory cortex silencing produces ASD-predominant features; extensive silencing across both regions produces the combined AuDHD presentation. [54] This model predicts that ADHD populations should show SST-14 silencing biomarkers at rates comparable to ASD populations — a testable hypothesis.

Testable Predictions

The two-layer model generates ten specific predictions testable in existing datasets and prospective studies:

- Plasma quinolinic acid should correlate with SST-14 peptide levels in ASD populations.
- The K:T ratio should predict clinical response to immunoglobulin therapy. [50]
- Lactate-to-pyruvate ratio should predict the State 1/State 2 boundary and the requirement for mitochondrial restoration in addition to immune clearance.
- Female ASD individuals should show higher SST-14 peptide levels than males with equivalent cytokine and autoantibody profiles.
- Autistic males with documented pubertal aromatase activity should show greater spontaneous improvement in SST-14-dependent outcomes than those without.
- ADHD populations should show elevated K:T ratios, cytokine profiles, and autoantibody titers at rates comparable to ASD populations.
- Children who develop IDA should show a higher constitutional susceptibility burden score (number of variant tipping points) than age-matched ASD children without the IDA biomarker signature.
- Plasma omega-3 PUFA levels and ALOX pathway capacity should predict whether LPS-driven inflammation resolves acutely or becomes chronic in prospective birth cohort studies.
- KMO variant status should predict the QUIN/KYNA ratio in ASD children with active IDO1 activation, independent of IDO1 activity level.
- DPP-IV activity measured in early infancy should predict adenosine clearance vulnerability before any dietary peptide or xenobiotic exposure and should correlate with subsequent IDA biomarker trajectory.

Proxy estimates from comorbidity cluster data suggest 20–30% of the ASD population may belong to the IDA biomarker subgroup — conservatively 250,000–400,000 US children. This is a provisional proxy estimate based on overlapping comorbidity prevalence data, not a directly measured figure, and requires validation through prospective biomarker-stratified cohort studies before any clinical or policy conclusions can be drawn from it.

Implications Beyond ASD

Gastric acid production declines progressively with age through atrophic gastritis, recreating key upstream cascade elements. SST-14 interneuron loss is one of the earliest and most consistent neuropathological findings in Alzheimer's disease, preceding widespread amyloid and tau pathology. [68,69] The same A1 astrocyte polarization and loss of hevin/SPARCL1 synaptogenic support documented in IDA are prominent in AD. [20,70] Crohn's disease — chronic intestinal inflammation, barrier disruption, LPS translocation — activates the same IDO1-kynurenine axis, with elevated kynurenine pathway metabolites and reduced somatostatin signaling documented in Crohn's cohorts. [29]

The same constitutional susceptibility profile proposed for immune-derived autism — impaired SPM resolution capacity, compromised gut barrier integrity, and dysregulated oral tolerance establishment — may also underlie the atopic disease burden disproportionately documented in ASD populations. Food allergy, allergic rhinitis, asthma, and eczema co-occur with ASD at rates substantially above general population prevalence. The mechanistic account is parallel: ALOX variant-impaired SPM production reduces the Treg-supportive environment required for oral and airway tolerance establishment; gut and airway barrier compromise allows food and environmental antigens to be presented in a pro-inflammatory rather than tolerogenic context; and Th2 polarization from chronic cytokine elevation drives IgE production and mast cell sensitization. If correct, IMIG-stratified IDA trial populations should show disproportionately high atopic comorbidity rates, and IMIG response should correlate with atopic disease burden reduction as a secondary endpoint — a testable prediction that would substantially broaden the clinical significance of the trial.

These observations are presented as hypotheses arising from the model, not as established findings, and require prospective evaluation in each population independently.

Limitations and Scope

Mechanistic claims carry substantially different levels of empirical support. **Level 1** (multiple independent human ASD cohort studies): IDO1 activation and kynurenine pathway diversion; cytokine elevation; methylation biomarker abnormalities; SST-14 interneuron hypoactivity producing social deficits — now directly demonstrated in the Magel2 mouse model where optogenetic SOM interneuron activation rescues sociability. [54] **Level 2** (established molecular biology with ASD application): NF-κB-mediated CREB suppression via the somatostatin gene CRE; the Gq-mER estrogen compensatory axis; A1/A2 astrocyte polarization and reversibility. **Level 3** (in vitro binding demonstrations and indirect metabolomics): CD26/DPP-IV blockade by casomorphin and gliadorphin with resulting adenosine accumulation; methylation cycle impairment via methionine synthase inhibition. **Level 4** (mechanistically plausible; not yet prospectively tested in ASD): pepsin pH-dependence as the primary upstream initiating event; gut SST-28 overactivation as a direct cascade consequence; the SPM/ALOX inflammatory resolution tipping point. The constitutional susceptibility section is explicitly the most hypothesis-dense section of this document — most tipping point proposals carry Level 3–4 evidence and the compound susceptibility profile require prospective birth cohort validation before clinical deployment.

A direct challenge to any multi-insult cascade model is reverse causation: gut dysfunction, selective eating, and immune dysregulation in ASD could be consequences of the neurodevelopmental condition rather than initiating causes. This challenge is taken seriously. Three lines of argument support the proposed upstream directionality. First, the founding conditions described — C-section delivery, formula feeding, antibiotic exposure, prenatal mercury and glyphosate exposure — precede ASD diagnosis by months to years and in several cases precede birth itself. These are not consequences of an existing neurodevelopmental state. Second, the Frye et al. folinic acid series [5,6,66] demonstrates prospectively that correcting a biochemical mechanism (folate receptor antibody-mediated methylfolate delivery failure) in a biomarker-selected subgroup produces behavioral recovery — which is consistent only with the biological cascade being upstream of the phenotype, not downstream of it. Third, the gut-brain axis directionality proposed here — gut pH dysregulation producing systemic immune activation producing neuroinflammation producing SST-14 silencing — is structurally consistent with documented gut-first pathology in regressive autism populations, where gastrointestinal abnormalities frequently predate neuropsychiatric symptom onset. Reverse causation cannot be definitively excluded without prospective birth cohort studies, which the testable predictions section identifies as the required next step.

The model does not claim to explain all ASD. Primarily genetic subtypes — Fragile X, Rett syndrome, defined single-gene mutations, and the SHANK3/CNTNAP2/NRXN1/CHD8/ADNP class of synaptic and chromatin variants — involve mechanisms mechanistically independent of the immune-metabolic cascade. The convergence is downstream: SST-14 silencing, A1 astrocyte polarization, and hevin/SPARCL1 withdrawal represent a common pathway through which both immune-metabolic and genetic mechanisms arrive at similar phenotypic outcomes. Biomarker stratification — not phenotypic diagnosis — separates them for trial purposes. The immune-derived subgroup is defined by the upstream biomarker signature — elevated K:T ratio, cytokine elevation, homocysteine dysregulation, autoantibody panel positivity — not by phenotypic severity.

Conclusion

Immune-derived autism is produced by a converging multi-step biological cascade originating in gut pH dysregulation and arriving, through immune activation and metabolic disruption, at the silencing of SST-14 interneurons. The silencing simultaneously disrupts the coordinated release of

oxytocin, VIP, and secretin, producing the social, sensory, sleep, gastrointestinal, motor, and cognitive features of the ASD phenotype cluster. The cascade is self-reinforcing, sex-differentiated by a specific molecular mechanism involving the estrogen-cAMP-CREB-SST14 compensatory axis, and reversible in the subset of affected individuals where the silencing mechanism remains transcriptional rather than structural. The cascade propagates only in those whose constitutional susceptibility profile narrows the margin between insult and threshold across enough cascade steps simultaneously — and that profile is measurable.

Three decades of clinical trials have produced inconsistent results because they targeted downstream neuropeptide outputs rather than the upstream converging mechanism, enrolled biologically heterogeneous populations rather than the biomarker-defined subgroup, and failed to account for the constitutional susceptibility architecture that determines which patients can respond to which interventions. The two-layer model provides the mechanistic architecture required to correct all three failures: identifying the upstream target, defining patient selection criteria, and characterizing the constitutional susceptibility profile that determines intervention pathway.

> ***The right question is not whether a given therapy helps autism. It is whether this intervention, in this biomarker-defined patient, with this constitutional susceptibility profile, at this point in the cascade, addresses the mechanism that is active in those individuals with ASD.***

The cascade can be interrupted at its convergent node. The trial can be designed. The patients can be selected by biomarker and constitutional profile. The mechanistic architecture exists. What remains is to run the right trial in the right patients.

Companion document: Restoring the Somatostatin Signal in Immune-Derived ASD: Using IMIG, IVIG, and MSC Therapy as Parallel Pathways to Neuropeptide Cascade Recovery

Is available in the Research section at decodingautismnow.com

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