BeyondMold

CLINICAL PRIMER

CDR / ISRMT PHENOTYPE SERIES · NO. D

Phenotype D The Closed Gate

Opening the Gate — a neuroendocrine & integrated-stress-response treatment roadmap

A clinician-facing synthesis of the therapies used to move a patient who is biologically "stuck in defense" back into restoration — the all-safe neuropeptides (VIP, α-MSH/KPV, oxytocin), the agents that relieve the integrated stress response (GLP-1, forskolin, quercetin, NAC, and others), the autonomic work that signals safety, and the gated sequence that ties them together.

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ORIENTATION — HOW TO READ THIS PRIMER

How to read this primer

This document is the Phenotype D companion to the Beyond Mold phenotype series. It assumes the reader already works inside the CDR/ISRmt model and the four-phenotype classification — **A Stuck Alarm, B Drained Battery, C Worn-Out Defender, and D Closed Gate** — and that the staging baseline has already been run. Its single job is to lay out, in clinical detail, the therapies that move a Phenotype D patient through the last transition: out of conservation and into restoration.

Each therapy is presented the same way: **mechanism of action**, a practical **dosing** summary, the **side-effect / caution** profile, and a plain statement of **where it fits** in the sequence and how strong the evidence is. The agents are grouped by the lever they pull, not by drug class, because in this phenotype the lever is what matters.

> **Three honest framings before any prescribing.** First, much of what follows is mechanistically reasoned from preclinical and adjacent-population data rather than proven in randomised mold-illness cohorts — evidence grade is flagged for every agent. Second, every peptide here is used off-label and most are compounded; sourcing, prescriber oversight, and monitoring are assumed throughout. Third, and most important, this is the *last* phenotype to treat, not the first — nothing in this primer is safe to deploy while the alarm is still accurate.

THE CARDINAL RULE OF THIS PHENOTYPE

You cannot open the gate while the danger is real. If exposure is ongoing, the source is uncontrolled, or the inflammatory drivers are still climbing, the "closed gate" is not a malfunction — it is the correct response, and forcing it open with neuropeptides or ISR-relieving agents tends to flare the patient. The prerequisites section is therefore not preamble; it is a hard gate of its own.

01 — THE PHENOTYPE

What the Closed Gate actually is

Phenotype D is the patient whose drivers have largely been handled — exposure removed, binders run, infections addressed, engines no longer frankly depleted — and who nonetheless does not recover. The biology has cleared the threat but has not received, or cannot act on, the signal that the threat is over. In the language of the Cell Danger Response, the cell is held at the **Phase Two to Phase Three transition**: conservation will not hand off to restoration.

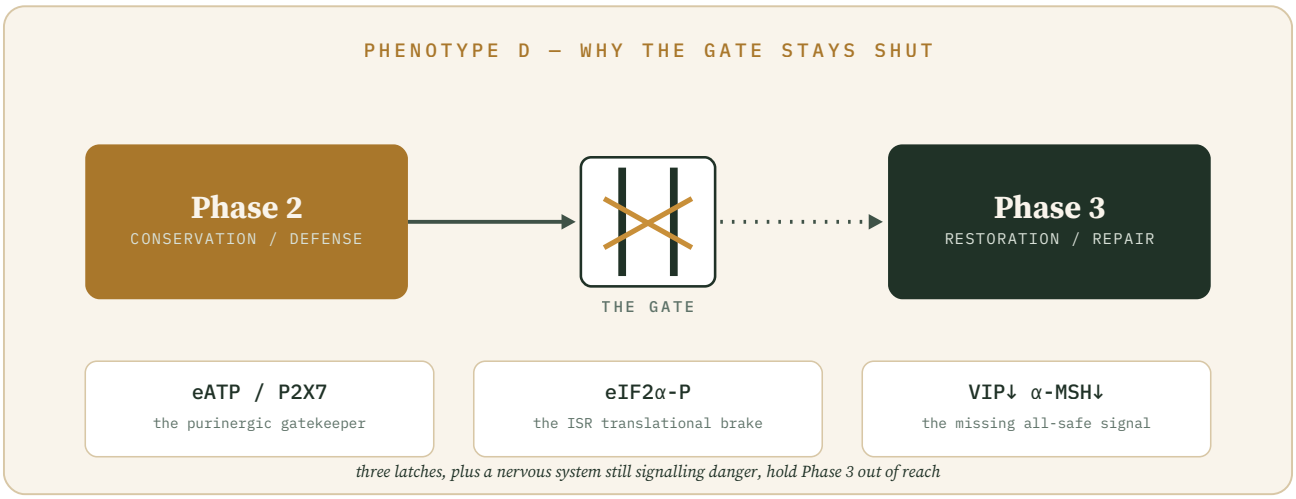

FIGURE 1. Phenotype D is a failure of the Phase 2→Phase 3 hand-off. Three molecular latches — the purinergic gatekeeper (eATP/P2X7), the integrated-stress-response brake (phosphorylated eIF2α), and a deficit of the all-safe neuropeptides (VIP, α-MSH) — together with an autonomic nervous system still broadcasting danger, hold restoration out of reach.

Mechanistically, four things keep the gate shut, and the treatment model maps directly onto them:

- **A persistent integrated stress response (ISRmt).** Phosphorylation of eIF2α by the stress kinases (PERK, GCN2, PKR, HRI) throttles cap-dependent translation to conserve resources. Adaptive when brief; pathological when it cannot terminate. Anabolic repair stays switched off.
- **A purinergic "keep-out" signal.** Extracellular ATP and related mitokines, read through P2X/P2Y receptors — P2X7 in particular acting as a gatekeeper — sustain the danger state and suppress normal cell-to-cell communication.
- **A neuroendocrine all-safe deficit.** The regulatory neuropeptides that signal "stand down" — VIP and α-MSH above all — are characteristically low, so even a quiet environment is not registered as safe.
- **An autonomic danger lock.** Parasympathetic withdrawal and low HRV keep the afferent tone of the body set to threat, reinforcing the cellular program from the top down.

MECHANISM NOTE

Why VIP and α-MSH are anchored to Phenotype D specifically: across the panel these two neuropeptides behave as the all-clear channel. In biotoxin illness VIP runs roughly 30–60% below normal, and α-MSH — the upstream melanocortin master regulator of mucosal defense, inflammation, and circadian and pain set-points — is depressed. Their deficiency is what distinguishes a gate that is shut for lack of signal (D) from an alarm that is still firing (A) or an engine that is still empty (B).

The Phenotype D laboratory signature

No single marker defines D; the pattern does. The cluster below is what tips classification toward the Closed Gate once the other phenotypes' drivers have been controlled.

Domain	Phenotype D pattern
All-safe neuropeptides	VIP low; α-MSH low — the defining pair, anchored to D.
ISRmt surrogates	GDF15 and/or FGF21 elevated out of proportion to a now-quiet exposure — the integrated stress response still broadcasting.
Residual inflammation	MMP-9, C4a and TGF-β1 trending *down* (drivers controlled) yet symptoms persist — the discordance that defines D.
Autonomic	Low resting HRV, blunted parasympathetic reactivity, poor recovery slope.
Endocrine downstream	Low ADH/osmolality dysregulation, suppressed sex steroids that track with VIP rather than primary gonadal failure.

02 — STRATEGY

The logic of opening the gate

Because the gate is held by both a *brake* and a *missing signal*, it opens to two complementary levers. Pulling only one tends to disappoint: relieve the stress response while the all-safe channel is still silent and the cell has permission but no instruction; supply the all-safe peptide while the ISR brake is still clamped and the instruction arrives at a cell that cannot yet translate it into repair.

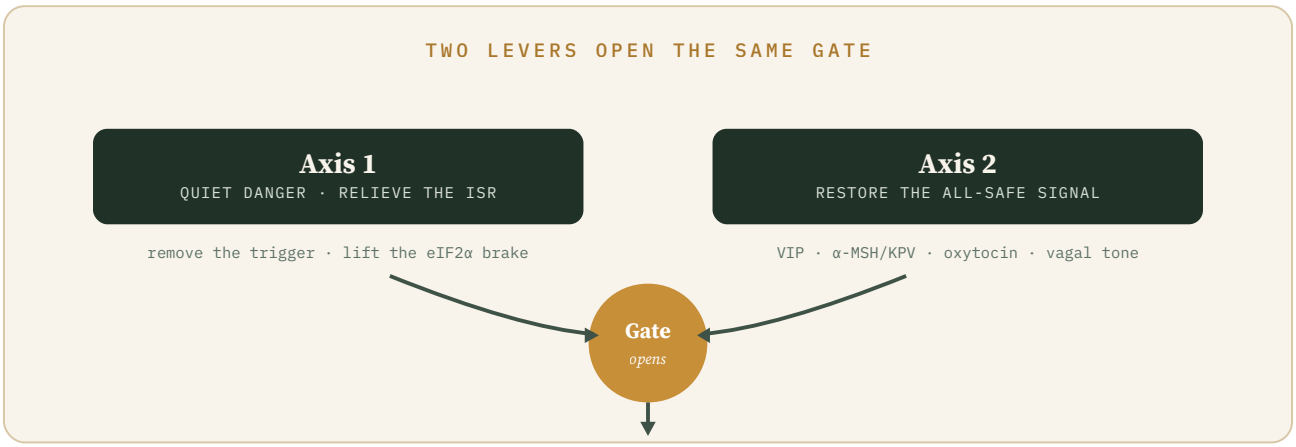

FIGURE 2. The two-axis strategy. Axis 1 quiets the residual danger signal and lifts the integrated-stress-response brake; Axis 2 restores the neuroendocrine and autonomic all-safe signal. Applied in sequence, on a foundation of confirmed safety, they let Phase 3 restoration resume.

The whole of this primer is organised around that figure:

- **Axis 1 — quiet the danger, relieve the ISR.** Lower what is still driving the stress kinases (residual exposure, oxidative load, purinergic signalling, microglial activation) and tip the eIF2α balance back toward dephosphorylation so translation — and with it anabolic repair — can resume.

- **Axis 2 — restore the all-safe signal.** Replace or re-induce the neuropeptides that say "stand down" (VIP, α-MSH via KPV, oxytocin) and rebuild the parasympathetic tone that carries the same message from the top down.
- **Then rebuild.** Once the gate is open, support the mitochondrial restoration that Phase 3 actually consists of, so the gain holds.

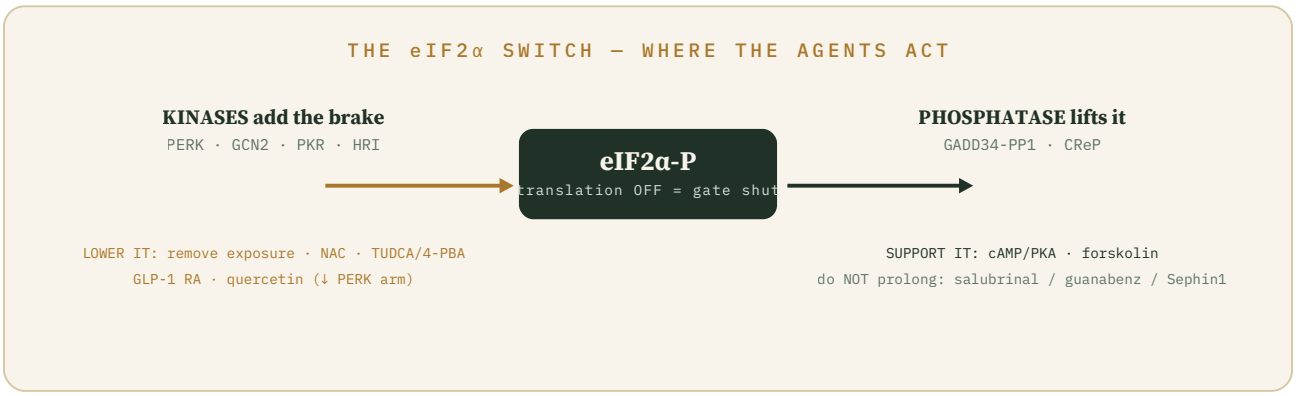

FIGURE 3. The eIF2α switch, with each agent mapped to where it acts. Most deployable tools work by lowering the kinase drive (left) rather than by directly forcing the phosphatase; agents that prolong eIF2α-P (salubrinal, guanabenz, Sephin1/raphin1) are protective in other diseases but are the wrong direction here and are noted only to be avoided.

03 — THE GATE YOU MUST EARN

Prerequisites — before any gate-opening agent

Every therapy in this primer assumes the patient has earned the right to it. This mirrors the Shoemaker sequencing logic for VIP — the all-safe peptide is the *final* step, and the most common cause of a "non-response" is an unmet prerequisite, not an ineffective drug. The checklist below is the entry gate for the entire Axis 1/Axis 2 sequence.

Prerequisite	Confirmed by	Why it gates everything downstream
Exposure removed & verified	ERMI / HERTSMI-2 in range; no second uncontrolled environment (home, work, vehicle)	An accurate alarm should not be silenced. Opening the gate into ongoing exposure reliably flares the patient.
Binder / clearance phase done	Adequate sequestration completed; symptoms stabilised	Circulating biotoxin keeps the kinase drive high; the ISR will re-clamp.
Source control	MARCoNS / occult infection addressed; sinus and gut handled	A persistent inflammatory nidus re-activates P2X7 and the stress kinases.
Inflammatory markers trending down	MMP-9, C4a, TGF-β1 falling on serial draws	Direction matters more than absolute value — the drivers must be receding, not rising.

Prerequisite	Confirmed by	Why it gates everything downstream
Mitochondrial floor	No frank Phenotype B depletion; basic cofactors repleted	Restoration is anabolic and energy-costly; an empty engine cannot execute the repair the gate permits.

> **Read the discordance as the green light.** The moment to open the gate is precisely when the drivers are *controlled and falling* but the patient remains ill — inflammatory markers receding while VIP/α-MSH stay low and ISR surrogates stay high. That mismatch is the signature that what remains is a signalling problem, not an active threat.

04 — AXIS 1

Quieting the danger signal & relieving the ISR

Axis 1 has two jobs that reinforce each other: turn down whatever is still activating the stress kinases, and tip the eIF2α balance back toward dephosphorylation so translation can resume. In practice the first does most of the work — the cleanest way to lift the brake is to stop pressing it.

The purinergic gatekeeper — eATP & P2X7 CONCEPTUAL TARGET

Naviaux's framework places extracellular ATP at the centre of the persistent CDR: inside the cell ATP is fuel, but outside it is a danger signal, read through P1/P2X/P2Y receptors, with **P2X7 behaving as a gatekeeper** of the danger state. Sustained eATP signalling is, mechanistically, one of the latches on our gate — it keeps cells in a defensive, poorly-communicating mode. This is the conceptual target that unifies Axis 1; the agents below are the deployable ways to lower it.

MECHANISM NOTE

Antipurinergic proof-of-concept: in mouse models and a small human trial (SAT1), a single low dose of the non-selective purinergic antagonist **suramin** — blood levels of only ~5–15μM — transiently reversed core features of the cell danger state. It is cited here strictly as mechanism validation, *not* as a clinical tool: suramin cannot be used long-term (anemia, adrenal toxicity), its effect washes out in weeks, and it remains investigational. It tells us the gate *can* be opened at the purinergic level; it does not tell us to prescribe it.

Low-dose naltrexone (LDN) DEPLOYABLE · MICROGLIA / TLR4

Mechanism. At 1–5 mg, naltrexone acts largely outside its classical opioid antagonism: it antagonises **Toll-like receptor 4 (TLR4) on microglia**, damping the activated-glia state that sustains neuroinflammation and central sensitisation, and lowering IL-1β, IL-6 and TNF-α. A second, transient opioid-receptor blockade produces a

rebound rise in endogenous endorphins. For Phenotype D it is the most practical lever on the microglial arm of the danger signal.

Dosing. Start 1.5 mg at bedtime; titrate by 1.5 mg every 1–2 weeks to a usual 3–4.5 mg qHS. Some patients do better dosing in the morning if sleep is disrupted, or splitting the dose. Compounded to allow low strengths.

Side effects / cautions. Vivid dreams and transient sleep disturbance early (often dose-timing dependent); occasional headache. Will precipitate withdrawal in anyone on opioid agonists — a true contraindication. Otherwise well tolerated and inexpensive.

Where it fits. Early in Axis 1, as a low-risk background that quiets microglial danger signalling before peptides are introduced.

Evidence: B — positive small RCTs in fibromyalgia, Crohn's, MS; extrapolated, not proven, in biotoxin illness.

The eIF2α / GADD34 axis — what "relieving the ISR" means TARGET EXPLAINER

The integrated stress response is governed by a single phosphorylation switch. Stress kinases phosphorylate eIF2α, which blocks the guanine-nucleotide-exchange factor eIF2B and shuts down general translation. The response is terminated by **dephosphorylation** of eIF2α through protein phosphatase 1 directed by two regulatory subunits — the stress-induced **GADD34 (PPP1R15A)** and the constitutive CReP (PPP1R15B). GADD34 is itself switched on downstream of the ISR as the built-in negative-feedback off-switch that restores protein synthesis once stress resolves.

MECHANISM NOTE

Two honest clarifications that shape every dosing decision below. (1) "GADD34 agonist" is loose shorthand: GADD34 is already the endogenous off-switch, and no clean, selective, clinically-available GADD34 inducer exists. What the deployable agents actually do is *lower the kinase drive* (so less eIF2α gets phosphorylated) or raise cAMP/PKA tone (which favours the phosphatase arm); the research tool **ISRIB** bypasses the brake entirely by restoring eIF2B function. (2) Direction matters: **salubrinal, guanabenz, and Sephin1/raphin1 do the opposite** — they inhibit GADD34 to *prolong* eIF2α-P. They are protective in proteostasis-overload diseases but are the wrong direction for opening this gate, and are listed only so they are not reached for by analogy.

Agents that lower the ISR drive

These are the "GADD34-side" tools in the practical sense defined above — they take pressure off the eIF2α brake by reducing the upstream stressors (oxidative, ER, inflammatory) or by raising cAMP/PKA tone. None is a magic ISR switch; together they shift the balance toward translational recovery.

GLP-1 receptor agonists PERK-ARM / NEUROINFLAMMATION

Mechanism. Beyond incretin action, GLP-1 receptor agonists reduce **PERK–eIF2α–CHOP** ER-stress signalling and raise the protective chaperone GRP78, while damping microglial and macrophage inflammation; GLP-1 receptors are expressed on neurons, astrocytes and microglia. The net effect is less of the very signalling that keeps the gate's ISR latch engaged, plus a genuine neuro-protective profile.

Dosing. Standard agents and titrations (e.g. semaglutide, liraglutide, dulaglutide, or dual GIP/GLP-1 tirzepatide), uptitrated slowly. In Phenotype D the goal is the lowest dose that yields the anti-inflammatory / ISR effect, not aggressive weight loss.

Side effects / cautions. Nausea and GI upset on uptitration; rare pancreatitis; gallbladder events; contraindicated with personal/family medullary thyroid carcinoma or MEN2. **Phenotype-specific caution:** in a low-reserve or lean CDR patient, drug-induced anorexia and lean-mass loss can *worsen* the Drained-Battery substrate — weigh against Axis 1 benefit and protect protein intake and resistance load.

Evidence: B — consistent preclinical ER-stress/neuroinflammation data and strong human cardiometabolic/neuro signals; ISR-relief use in biotoxin illness is inferential.

Forskolin CAMP / PKA → PHOSPHATASE ARM

Mechanism. A direct adenylyl-cyclase activator that raises **cAMP–PKA** tone; cAMP signalling favours eIF2α dephosphorylation and the GADD34–PP1 arm, and is broadly anti-inflammatory. It is the closest oral tool to "pushing" the phosphatase side of the switch rather than only easing the kinases.

Dosing. Standardised *Coleus forskohlii* extract (typically 10–20% forskolin), commonly ~250 mg of a 10% extract once or twice daily (i.e. ~25–50 mg forskolin/day). Bioavailability is modest; effects are gentle.

Side effects / cautions. Vasodilation — can lower blood pressure and is additive with VIP and antihypertensives; increases gastric acid (caution with ulcers); theoretical bleeding risk with anticoagulants; tachycardia at higher intakes.

Evidence: C — mechanistically attractive, largely preclinical for the ISR claim; use as an adjunct, not a centrepiece.

Quercetin ER STRESS · MAST-CELL · SENOLYTIC

Mechanism. A flavonoid with three convergent actions useful here: it attenuates **PERK–CHOP ER-stress** signalling and oxidative load, it **stabilises mast cells** (directly relevant to the MCAS overlap common in this population), and it has senolytic activity. It lowers several of the inputs that keep eIF2α phosphorylated.

Dosing. 500 mg once or twice daily; absorption improves with a phytosome / bromelain co-formulation. Senolytic protocols use intermittent high-dose pulses but that is a separate, more aggressive use-case.

Side effects / cautions. Generally well tolerated; high chronic doses raise theoretical renal and thyroid-peroxidase concerns; inhibits CYP3A4/P-gp (check interacting drugs); mild headache or GI upset.

Evidence: C — solid for mast-cell stabilisation; ISR/ER-stress effect is mechanistic. A reasonable low-risk background agent.

N-acetylcysteine (NAC) GLUTATHIONE · REDOX

Mechanism. A glutathione precursor that lowers the oxidative load which activates the eIF2α kinases (HRI, PKR and the PERK arm respond to ROS). By restoring redox headroom it reduces the drive onto the brake and supports mitochondrial glutathione — a quiet but real Axis 1 contribution.

Dosing. 600–1200 mg once or twice daily (600–1800 mg/day typical); take with food.

Side effects / cautions. GI upset, occasional sulphur odour; rare bronchospasm in asthmatics at high doses; theoretical additive effect with nitrates/antihypertensives. Very wide safety margin.

Evidence: B for redox/glutathione repletion; ISR-specific benefit inferred.

Chemical chaperones — TUDCA & 4-PBA UPSTREAM ER STRESS

Mechanism. Tauroursodeoxycholic acid (TUDCA) and sodium phenylbutyrate (4-PBA) are chemical chaperones that improve protein folding and directly reduce the **ER-stress drive onto PERK**, lowering eIF2α phosphorylation at its source. 4-PBA is also an HDAC inhibitor. They target the same upstream node as GLP-1 but by a different route.

Dosing. TUDCA ~250–500 mg once or twice daily (also hepatobiliary supportive). 4-PBA is a prescription agent with a heavier tolerability and taste burden; TUDCA is the more practical outpatient chaperone.

Side effects / cautions. TUDCA: loose stools, mild GI. 4-PBA: significant sodium load, strong taste, GI upset — reserve for deliberate use.

Evidence: C — strong preclinical ER-stress reduction; TUDCA reasonable as a gentle adjunct.

Background redox / Nrf2 support ADJUNCT

Sulforaphane (broccoli-sprout extract), curcumin, and similar Nrf2 activators raise endogenous antioxidant and chaperone capacity, lowering the same oxidative inputs that keep the ISR engaged. Treat as low-risk background rather than primary movers. Evidence: C

> **One agent class to avoid here.** Salubrinal, guanabenz, and Sephin1/raphin1 *prolong* eIF2α phosphorylation by inhibiting GADD34. They are being developed to *sustain* the ISR brake in proteostasis diseases — the exact opposite of the Phenotype D goal. Do not reach for them to "modulate the ISR."

05 — AXIS 2

Restoring the neuroendocrine all-safe signal

Axis 2 supplies the instruction the cell is waiting for. These are the regulatory neuropeptides that mean "stand down" — depleted in Phenotype D, and replaceable. VIP is the centrepiece; KPV stands in for the α-MSH

channel; oxytocin adds the social-safety and parasympathetic dimension. All are introduced *after* Axis 1 has quieted the danger drive, never before.

Vasoactive intestinal peptide (VIP) THE CENTREPIECE · LAST STEP

Mechanism. A 28-amino-acid neuropeptide signalling through **VPAC1 and VPAC2** receptors across immune cells, lung, gut, vasculature and CNS. It is a master pro-resolution signal: it shifts cytokine balance away from inflammation, generates $CD4^+$ $CD25^+$ $Foxp3^+$ regulatory T cells, lowers pulmonary artery pressure, and supports grey-matter and endocrine recovery. In biotoxin illness VIP is characteristically 30–60% below normal, and restoring it is, in effect, re-supplying the all-clear channel that defines this phenotype.

Dosing & route. The published Shoemaker protocol is **intranasal, 50µg per metered spray, four times daily** (the very short plasma half-life drives the frequent dosing), with a 30-day initial endpoint and extended courses for grey-matter restoration. A subcutaneous route (~50µg AM/PM, often cycled) is also used. Compounded by prescription.

MECHANISM NOTE

Route as a differentiation point. The intranasal-VIP method sits within an existing patent estate (US 9,770,170 B2). A **buccal/sublingual delivery route** is therefore of specific interest in this program both clinically (mucosal absorption, patient acceptability) and as a deliberately distinct delivery construct from the intranasal claim. Any route decision should be made with current freedom-to-operate guidance in hand.

Side effects / cautions. Generally excellent tolerability. Transient hypotension and flushing (VIP is a vasodilator — start low in low-baseline-BP patients; additive with forskolin and antihypertensives), mild nasal irritation (intranasal), and loose stools / secretory diarrhoea at higher doses (the "intestinal" in its name). Use caution with active malignancy given pro-angiogenic and immunomodulatory properties. Early transient symptom-flare usually signals an unmet prerequisite, not a true VIP intolerance.

Where it fits. The *final* agent, deployed only once exposure is verified clear, source control is achieved, and inflammatory markers are falling. A poor VIP response is, far more often than not, a missed environmental source or incomplete prerequisite.

Evidence: B in CIRS (Shoemaker cohort data and documented biomarker shifts); broader anti-inflammatory pharmacology well established.

α-MSH & the melanocortin system THE DEFICIT · MOSTLY INDIRECT

Mechanism / problem. α-melanocyte-stimulating hormone is the upstream melanocortin regulator of inflammation, mucosal and antimicrobial defense, and circadian, appetite and pain set-points — and it is characteristically low in this population. There is, however, **no practical direct α-MSH replacement**: full melanocortin agonists (melanotan II, afamelanotide) carry pigmentary, cardiovascular and off-target effects that make them inappropriate here. The clinically useful moves are to *re-induce* endogenous α-MSH by remov-

ing its upstream suppression (the prerequisite work, plus VIP restoration, which tends to pull α-MSH up with it) and to supply its anti-inflammatory message through its active fragment, KPV.

KPV (Lys-Pro-Val) DEPLOYABLE A-MSH PROXY

Mechanism. KPV is the C-terminal tripeptide of α-MSH that **retains the anti-inflammatory activity without the pigmentary or appetite effects** of the parent hormone. It acts largely receptor-independently — entering cells and inhibiting IκB kinase to block **NF-κB** nuclear translocation, with additional inflammasome (IL-1β/IL-18) and MAPK damping and reduced ROS. It also strengthens epithelial barriers, which is why it is favoured for the gut and skin overlap. Effectively, it carries the α-MSH "stand-down" message into the cell.

Dosing. Unusually for a peptide it is **orally bioavailable**; common use is ~200–500µg/day oral (capsule), with subcutaneous and topical routes also used (topical for skin, oral for gut-centric inflammation).

Side effects / cautions. Very well tolerated in available data; mild injection-site or GI effects. Human data are limited — most evidence is animal and cell-culture.

Where it fits. The practical α-MSH-channel restorer, reasonable to begin alongside or just before VIP as a gentler anti-inflammatory primer.

Evidence: C — compelling preclinical (colitis, dermatitis, systemic inflammation); minimal direct human trial data.

Oxytocin SOCIAL SAFETY · VAGAL · ANTI-INFLAMMATORY

Mechanism. Oxytocin is the neuroendocrine bridge between Axis 2 and the autonomic work that follows. It is directly anti-inflammatory — suppressing **NF-κB** and lowering IL-1β, IL-6 and TNF-α, including in activated microglia — while **dampening HPA-axis output** and raising parasympathetic (vagal) tone. It is, in the most literal sense, a chemical "you are safe with others" signal, and it reaches the same NF-κB and microglial targets as KPV from a different direction.

Dosing. Intranasal, typically ~10–24 IU as needed or once-twice daily; compounded. Effects are acute and well suited to pairing with the autonomic / relational-safety work below.

Side effects / cautions. Generally mild — nasal irritation, occasional headache, transient mood/sensitivity shifts. Theoretical caution in pregnancy (uterotonic) and with hyponatraemia risk at high/frequent dosing. Avoid framing it as a primary anti-inflammatory; its value here is the combined safety/vagal/anti-inflammatory profile.

Evidence: C — robust preclinical anti-inflammatory and vagal data; human data strongest for social/affective and stress-axis effects.

PACAP VIP COUSIN · USE WITH CAUTION

Pituitary adenylate cyclase-activating polypeptide shares VIP's receptors (VPAC1/2, plus PAC1) and much of its cAMP-driven, neurotrophic, anti-inflammatory biology, making it conceptually adjacent to VIP. The important caution is that PACAP is also a validated **migraine and stress-axis trigger** in susceptible patients, so it is not a

clean VIP substitute and should be approached carefully, if at all, in a population prone to headache and autonomic lability. Evidence: D for this indication — mechanistic only.

Adjacent peptides — honorable mentions

These do not target the gate's core latches but are commonly stacked for the comorbidity profile. Each is flagged for its (limited) evidence so it is not over-promised.

- **Thymosin α-1.** Immune-regulatory; retrains T-regulatory balance and is used to correct the dysregulated immune set-point that underlies the illness. Subcutaneous, e.g. ~1.6 mg twice weekly over 12–16 weeks. A reasonable immune-axis adjunct. Evidence: C
- **BPC-157.** A "body-protective" peptide popular for gut and connective-tissue repair (angiogenesis, nitric-oxide pathways). It is a *restoration-phase* tool, not an all-safe signal, and human data are minimal. Use, if at all, once the gate is open. Evidence: D
- **Semax / Selank.** Melanocortin/ACTH-fragment and tuftsin-derived neuropeptides with neurotrophic (BDNF) and anxiolytic profiles; conceptually in the neuroendocrine-safety family and sometimes used for the cognitive/affective residue. Evidence: D

> **How these three axes combine in practice.** KPV and oxytocin make sensible *primers* — gentle, broadly anti-inflammatory, low-risk — introduced as Axis 1 is quieting the danger drive. VIP is the keystone, reserved for last. Thymosin α-1 sits alongside as immune retraining; BPC-157 and the rest belong to the rebuild that follows, not the opening itself.

06 — AXIS 2, CONTINUED

The non-pharmacologic all-safe signal

The same "stand-down" message the peptides carry chemically can be generated as an afferent signal by the nervous system itself — and in Phenotype D it must be, because an autonomic system locked in threat will keep re-closing the gate the peptides are trying to open. This is biology, not adjunct: the cholinergic anti-inflammatory pathway lowers the same NF-κB-driven cytokines as KPV and oxytocin.

- **HRV resonance breathing.** Slow paced breathing near ~6 breaths/min brings respiration, heart rhythm and blood pressure into coherence — the most reliable safety signal a patient can generate on demand. With a biofeedback device it is, in effect, vagal strength training. This is also where the **HRV–VIP–α-MSH relationship** becomes practical: rising HRV is an accessible read-out that the all-safe channel is coming back online.
- **Transcutaneous vagal stimulation (taVNS).** Auricular vagal stimulation tones the same pathway without requiring a learned breathing skill — useful for patients who cannot yet self-regulate.

- **Relational & oxytocinergic safety.** Warmth, co-regulation and felt social safety raise endogenous oxytocin and parasympathetic tone — the behavioural complement to intranasal oxytocin.
- **Sleep & glymphatic clearance, light & circadian anchoring, graded movement.** Deep sleep restores the clearance and anabolic windows; morning light re-anchors the circadian set-points that α-MSH governs; sub-maximal graded movement rebuilds capacity without triggering push-crash.

> **Why this belongs inside Axis 2, not after it.** Pairing the peptides with autonomic safety work is what makes the gain hold. VIP or oxytocin given to a body whose afferent tone still reads "danger" is a signal arriving where the alarm is still sounding. Raise vagal tone in parallel and the chemical and neural all-safe signals reinforce each other.

07 — AFTER THE GATE OPENS

Rebuilding — what Phase 3 actually consists of

Opening the gate grants *permission* to repair; it does not perform the repair. Phase 3 is anabolic and mitochondrial, and if the substrate isn't supported the patient stalls just past the threshold. Once translation is restored and the all-safe signal is in place, support the rebuild:

Lever	Agents	Role in restoration
NAD^+ capacity	NR or NMN; niacinamide	Restores the redox/repair currency depleted in the danger state.
Electron transport	CoQ10/ubiquinol; PQQ	Bioenergetic support and mitochondrial biogenesis signalling.
Mitophagy / quality control	Urolithin A; spermidine	Clears damaged mitochondria so new capacity is healthy capacity.
Energetic buffers	Creatine; magnesium; carnitine	Phosphate buffering, enzymatic cofactors, fatty-acid transport.
Cofactor floor	B-complex (B1/B2/B6/B12), folate	One-carbon and TCA cofactors the rebuild runs on.

This is also where measurable bioenergetics earn their place: **spare respiratory capacity on a Seahorse assay** objectivises the reserve that should now be climbing, while GDF15/FGF21 should recede as the ISR releases — the same discordance that opened the chapter, now resolving.

08 — THE ROADMAP

A sequenced protocol to open the gate

The agents above only work in order. The sequence below is gated — each stage has an entry condition and an exit criterion, and the most powerful tool (VIP) is reached only when the stages beneath it are secure. This is the same discipline that makes the Shoemaker VIP endpoint reliable, generalised to the whole Axis 1/Axis 2 model.

ENTRY TO THE ENTIRE SEQUENCE: Phenotype D confirmed · drivers controlled and falling · VIP/α-MSH low with persistent symptoms

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Confirm the prerequisites — THE HARD GATE

Do not proceed while the alarm is still accurate. Re-hunt for a missed environmental source (workplace, vehicle, second residence) before anything else. This stage is itself a gate.

EXIT GATE: Exposure verified clear; source control done; MMP-9 / C4a / TGF-β1 falling on serial draws; no frank Phenotype B depletion.

1

Quiet the danger & lay the autonomic foundation — AXIS 1 + VAGAL

Begin LDN titration and the redox/ISR-drive background (NAC, quercetin, ± TUDCA). Start HRV resonance breathing ± taVNS daily. Optimise sleep, light, graded movement. Consider a low-dose GLP-1 RA where metabolically appropriate.

EXIT GATE: Microglial/danger drive trending down; HRV beginning to rise; patient tolerating background agents.

2

Relieve the ISR & prime the all-safe channel — AXIS 1 + EARLY AXIS 2

Add the gentler neuroendocrine primers — KPV (α-MSH channel) and intranasal oxytocin — alongside the Axis 1 background ± forskolin for cAMP tone. Thymosin α-1 here if immune retraining is indicated.

EXIT GATE: Symptom stability without flares; inflammatory markers low-and-steady; autonomic reactivity improving.

3

Open the gate — VIP — THE KEYSTONE

Introduce VIP only now, on the secured foundation. Intranasal 50µg QID (or SubQ AM/PM), starting low if BP is low. An early flare means re-check prerequisites — it is rarely the peptide.

EXIT GATE: Day-30 reassessment: biomarker shift (e.g. falling C4a/TGF-β1), QoL gain, no exposure-driven flare.

4

Consolidate the restoration PHASE 3 REBUILD

Support the mitochondrial rebuild (NAD^+ , CoQ10/PQQ, urolithin A, creatine, cofactors). Taper the scaffolding as endogenous VIP/α-MSH and HRV normalise. Maintain environmental vigilance.

EXIT GATE: Rising spare respiratory capacity; GDF15/FGF21 receding; durable symptom resolution off escalating support.

If a stage flares the patient, step back a stage. A flare is information, not failure — almost always an unmet prerequisite, a re-exposure, or moving too fast. The correct response is to drop back to the previous gate, re-secure it, and re-advance, not to push harder against a gate the biology is telling you is not ready.

09 — AT A GLANCE

Master summary — every agent on one page

A consolidated reference. Evidence grades are deliberately conservative: (A) RCT-level in this/closely-adjacent indication · (B) good human data, extrapolated here · (C) mechanistic + preclinical, limited human · (D) mechanistic / experimental only.

Agent	Axis · lever	Mechanism (one line)	Typical dosing	Key cautions	Ev.
Low-dose naltrexone	1 · microglia/ TLR4	TLR4 antagonism dampens activated glia; endorphin rebound	1.5→3–4.5mg qHS	Vivid dreams; opioid agonists contraindicated	B
GLP-1 RA	1 · PERK arm	↓ PERK-eIF2α-CHOP ER stress; ↓ neuroinflammation	low, slow titration	GI; lean-mass loss in low-reserve patients; MTC/MEN2	B
Forskolin	1 · cAMP/PKA	↑ cAMP favours eIF2α dephosphorylation; anti-infl.	~25–50mg/d (10% ext.)	Hypotension (additive w/ VIP); gastric acid	C
Quercetin	1 · ER stress/ mast cell	↓ PERK-CHOP & ROS; mast-cell stabiliser; senolytic	500mg 1–2×/d	CYP3A4/P-gp inhibition; high-dose renal/ thyroid	C
NAC	1 · redox	Glutathione precursor; ↓ oxidative kinase drive	600–1200mg 1–2×/d	GI; rare bronchospasm	B
TUDCA / 4-PBA	1 · ER chaperone	Chemical chaperone ↓ PERK drive at source	TUDCA 250–500mg 1–2×/d	Loose stools; 4-PBA sodium load/taste	C

Agent	Axis · lever	Mechanism (one line)	Typical dosing	Key cautions	Ev.
VIP	2 · all-safe (keystone)	VPAC1/2 pro-resolution; ↑ Treg; restores the deficit	IN 50µg QID (or SubQ AM/PM)	Hypotension/flush; loose stool; malignancy caution; **last step**	B
KPV	2 · α-MSH proxy	↓ IKK→NF-κB; inflammasome; barrier repair	~200–500µg/d oral	Limited human data; mild GI/site	C
Oxytocin	2 · safety/vagal	↓ NF-κB/cytokines; ↓ HPA; ↑ vagal tone	IN ~10–24 IU	Pregnancy (uterotonic); hyponatraemia at high dose	C
Thymosin α-1	2 · immune retraining	Re-balances T-regulatory set-point	~1.6mg SubQ 2×/wk	Generally well tolerated; limited RCTs	C
PACAP	2 · VIP cousin	VPAC/PAC1 cAMP, neurotrophic	cautious / experimental	**Migraine & stress-axis trigger**	D
Suramin	1 · purinergic (proof)	Non-selective P2 antagonist; ends CDR transiently	investigational only	Anemia, adrenal toxicity; not for clinical use	D

Restoration-phase agents (NAD^+ precursors, CoQ10/PQQ, urolithin A, creatine, cofactors; BPC-157) are summarised in Section 07 and are deployed after the gate opens rather than to open it.

10 — EVIDENCE, SAFETY & SOURCING

Evidence, safety & sourcing

This primer is a clinical synthesis, not a guideline. The mechanisms are well grounded; the *application* of several of them to biotoxin-illness Phenotype D is mechanistically reasoned and, in places, ahead of the trial evidence. That is stated plainly so it can be weighed in every prescribing decision.

- **Honest evidence grading.** Only VIP (in CIRS cohorts) and LDN/GLP-1 (in adjacent indications) rise to good human data; KPV, oxytocin, forskolin, quercetin, the chaperones and the adjacent peptides rest largely on preclinical and mechanistic support. The grades in the master table are deliberately conservative.
- **Off-label & compounded.** Every peptide here is used off-label, and most are compounded. Source from reputable compounding pharmacies with potency and sterility documentation; research-only material is not for human use.
- **Monitoring.** Track the markers that defined the phenotype — VIP/α-MSH, GDF15/FGF21, MMP-9/C4a/TGF-β1, HRV — on a sensible cadence, plus BP (VIP/forskolin), metabolic and GI tolerance (GLP-1), and sleep (LDN). Direction of travel matters more than any single value.

- **Contraindications to hold in view.** Opioid agonists with LDN; active malignancy with VIP; MTC/MEN2 with GLP-1 RAs; pregnancy with oxytocin and several peptides; additive hypotension across VIP + forskolin + antihypertensives; migraine-prone patients with PACAP.
- **The sequencing rule, once more.** The gate is opened last, on a secured foundation. Premature neuropeptide use into ongoing exposure or rising inflammation is the most common way this protocol goes wrong.

> **Scope.** This document supports clinician decision-making and education within the Beyond Mold CDR/ISRmt framework. It is not individualised medical advice, does not establish a standard of care, and does not replace prescriber judgement, informed consent, or appropriate monitoring for the individual patient in front of you.

Selected references

Paraphrased for orientation; consult the primary sources directly.

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