BeyondMold

CLINICAL FRAMEWORK

FOR CLINICIANS — NOT INDIVIDUAL MEDICAL ADVICE

The Cell Danger Response in Chronic Mold Illness

Mechanism, staging, and a phenotype-matched, sequence-gated protocol

Positioning CIRS as a validated special case of the CDR / ISRmt framework, governed throughout by *resolve before fortify*.

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00 · EXECUTIVE SUMMARY

The framework in one view

Five pathways, one checkpoint

CGRP, PACAP/VIP, P2X3, TRP and PGE2 converge — via two second messengers — on a single mitochondrial checkpoint: the Cell Danger Response.

One governing switch

The mitochondrial integrated stress response (ISRmt) — OMA1–DELE1–HRI → eIF2α-P → ATF4 — turns the CDR on, sustains it, and (via GADD34) releases it. “Stuck” = a non-terminating switch.

Stuck = arrhythmic

Read chronobiologically, the stalled CDR is a collapse of oscillation; CDR3 is the resumption of rhythm — measured by amplitude, not means.

Sequenced & phenotype-matched

Recovery is gated (resolve → restore → fortify) and the final push is matched to one of four phenotypes (A–D).

01 · PRIMARY SIGNALING

Five neurovascular danger pathways

Each sensor is tuned to a distinct survival-threat class; persistent or intense exposure recruits several in parallel — the substrate for convergence. A single water-damaged building trips four at once while depleting the resolution arm of the fifth.

Pathway	Receptor(s)	Inducing triggers	Threat class
CGRP	CLR · RAMP1 · RCP	Barometric drop, vasodilation, NO donors, shear	Vascular / mechanical
PACAP / VIP	PAC1 (danger) · VPAC1/2 (resolution)	Circadian disruption, sleep loss, anxiety, sensory overload	Autonomic / circadian

Pathway	Receptor(s)	Inducing triggers	Threat class
P2X3	Ionotropic, ATP-gated	Ischemia, hypoxia, cell lysis (spilled eATP)	Cell damage / hypoxia
TRP	TRPV1 · TRPA1	VOCs, formaldehyde, smoke, acidosis, thermal shock	Chemical / environmental
PGE2	EP1–EP4 via COX-2	Omega-6 surge, LPS/cytokines (IL-1β, TNF-α)	Systemic inflammation

> **The PACAP/VIP twist.** PACAP drives danger via PAC1; VIP is near-inert at PAC1 and acts at VPAC1/2 — the same axis carries both the alarm and its stand-down.

03 · THE BOTTLENECK

Two second messengers, one mitochondrion

The pathways begin at unrelated receptors but speak a shared intracellular language, intersecting at two hubs whose combined signal the mitochondrion reads as an unambiguous danger cue.

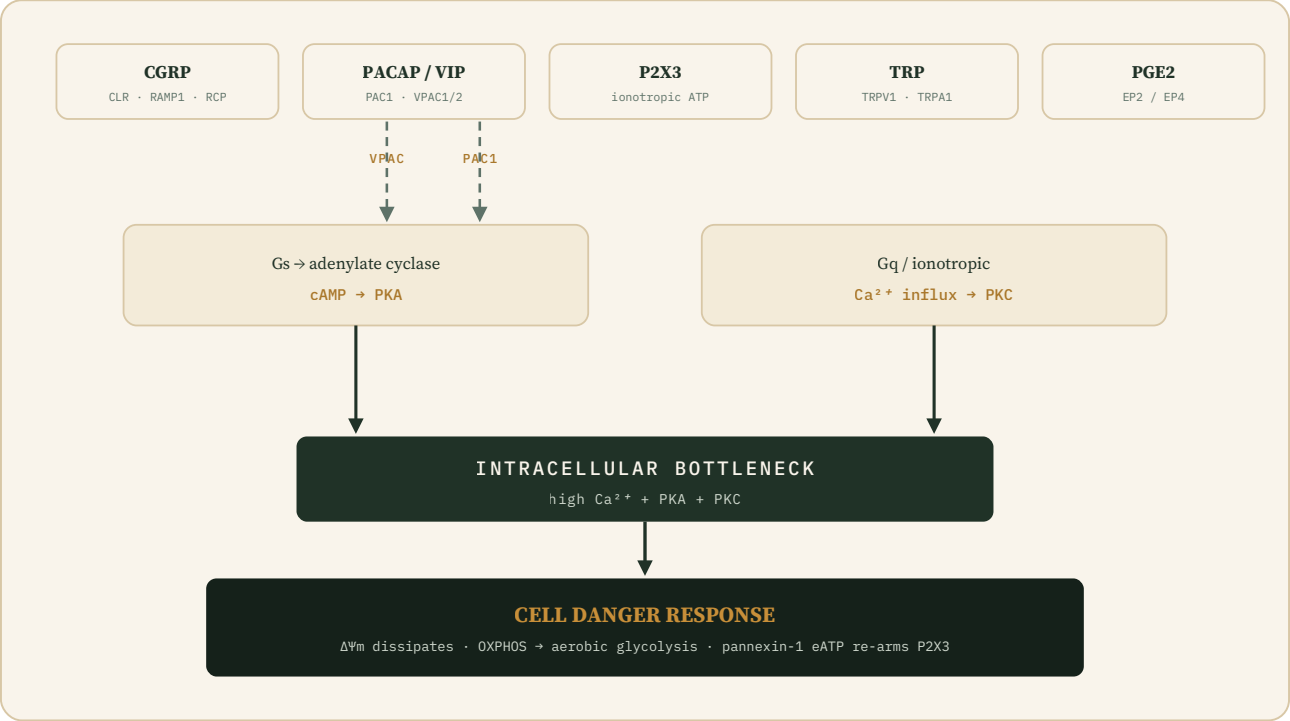

FIGURE 1. The cAMP/PKA arm (CGRP, VPAC1/2, PGE2-EP2/EP4) and the Ca²⁺/PKC arm (PAC1, P2X3, TRP) converge into a combined kinase/calcium signal. High matrix Ca²⁺ dissipates ΔΨm, OXPHOS gives way to aerobic glycolysis, and pannexin-1 eATP export re-arms P2X3 — self-amplifying by design.

04 · THE GOVERNING SWITCH

The ISRmt enacts the CDR

The pivot is not metaphorical. Loss of ΔΨm and proteotoxic stress activate the inner-membrane protease OMA1, which cleaves DELE1; cleaved DELE1 activates HRI (one of four eIF2α kinases). eIF2α-P at Ser51 collapses cap-dependent translation while selectively up-translating ATF4. GADD34–PP1 dephosphorylation terminates the response.

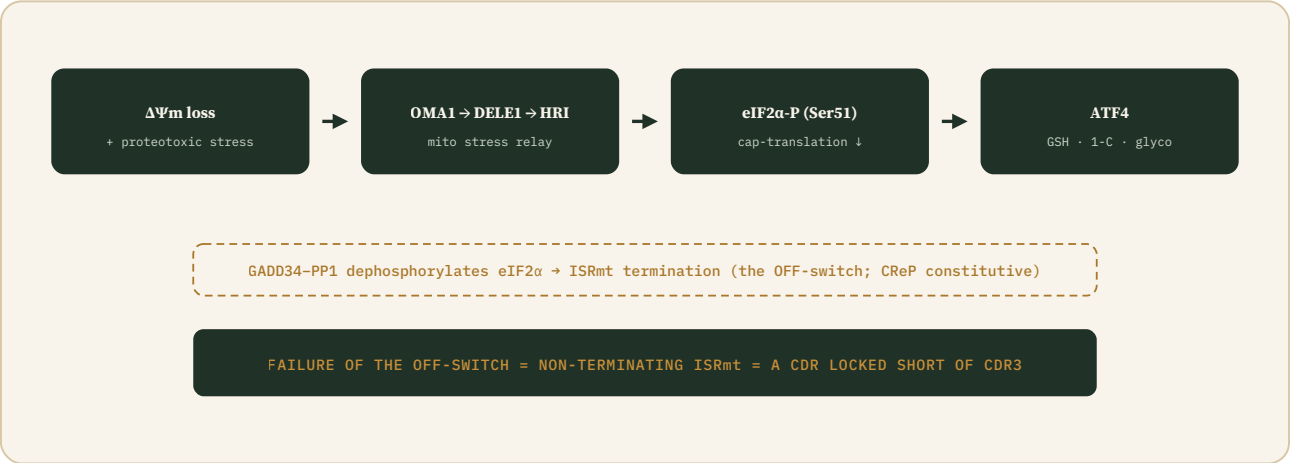

FIGURE 2. The ISRmt switch. A transient pulse is adaptive and self-terminating via GADD34–PP1; chronic, non-resetting eIF2α phosphorylation is the molecular lesion behind a stalled Cell Danger Response.

> **Two levers follow directly.** Reduce upstream danger drive, and restore the dephosphorylation / resolution signal (the VIP–VPAC arm).

02 · THE DANGER PROGRAM

Seasonal metabolism maps to the CDR phases

Naviaux's seasonal model lets an evolutionary account double as a clinical staging system: each metabolic mode has a master regulator and a CDR phase.

State	Season	Master regulator	Metabolic mode	CDR phase
Growth & repair	Summer	mTOR	Polymer synthesis; division	— (salugenesis)
Conservation	Winter	AMPK	Autophagy; efficiency	Early / recovery

State	Season	Master regulator	Metabolic mode	CDR phase
Acute threat	Storm	NF-κB · HIF-1α · Nrf2	ROS, purinergic, immune; growth halted	CDR1
Chronic siege	Endless winter	ATF4 · ISRmt · GDF15	Hypometabolism; OXPHOS↓, glycolysis↑	CDR2
Restoration	Spring	PGC-1α · BDNF · VIP	Biogenesis; M2 shift; repair	CDR3

> **CDR2 is intelligent triage, not failure** — but it is self-perpetuating, which is why it does not resolve on its own and requires coordinated intervention.

05 · ENERGETIC FAILURE

The non-terminating ISRmt & its readouts

A persistent CDR1/2 state inflicts structural and genetic damage on the very organelles needed to escape it: ongoing injury keeps OMA1–DELE1–HRI active, which keeps eIF2α phosphorylated, which keeps the cell in defense. A switch that will not turn off is a cycle that cannot close.

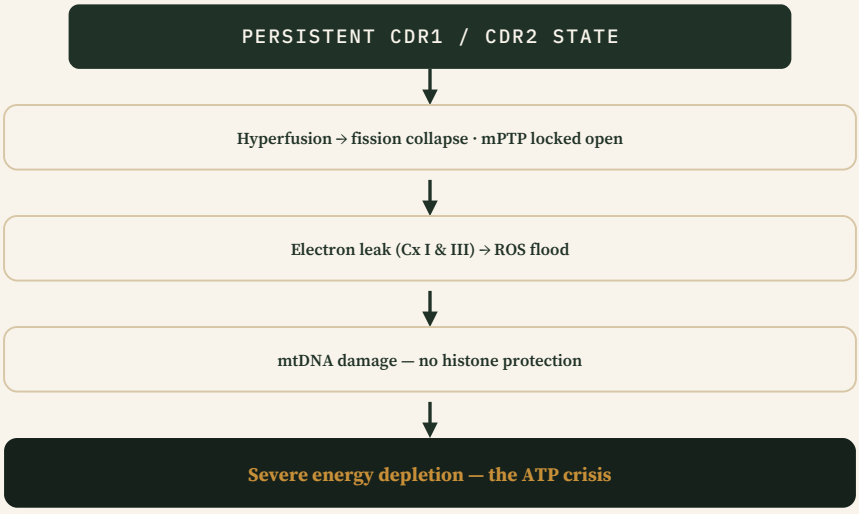

FIGURE 3. Structural degradation (fragmentation, pore opening), oxidative stress (ROS), and mtDNA mutation converge on a cell that needs ATP to clear calcium and repair itself but can no longer make it.

The clinical fingerprint

ATF4-driven mitokines GDF15 and FGF21 spill into the circulation as accessible readouts of a non-terminating ISRmt — a candidate biomarker axis for the stuck state itself rather than for any single upstream trigger. They are elevated in active CDR1/2 and normalize (with only transient challenge-rises) as the patient moves toward CDR3.

06–07 · EMERGENCY COMPENSATION

Maladaptive loops & lowered thresholds

To keep tissue alive through the energy crisis, three compensations each buy short-term function at the cost of long-term hyper-reactivity — converting a transient defensive state into a self-sustaining network.

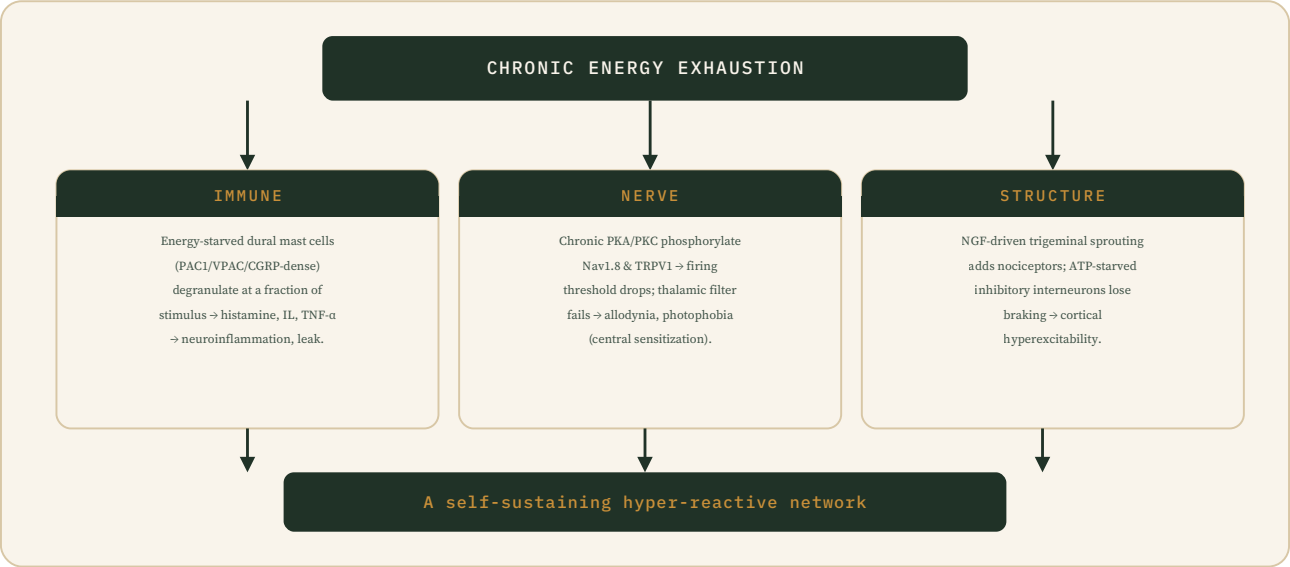

FIGURE 4. Immune, neural, and structural compensations each raise sensitivity. Together they convert a transient defensive state into a self-sustaining hyper-reactive network.

> **The threshold model.** The same stimulus — a barometric dip, a trace of perfume, an hour of lost sleep — is filtered by a replete system and ignites a full crisis in an energy-starved one.

THE CHRONOBIOLOGICAL REFRAME

CDR3 is not a level the system returns to — it is a rhythm it resumes

The stalled CDR is, in chronobiological terms, *arrhythmic* — oscillation collapsed into a flat defensive set-point. This converges with McEwen's allostatic load: chronic stress drives the HPA axis into a flattened, glucocorticoid-resistant hypocortisolism — too little rhythm, not too little cortisol. The stalled CDR and the flattened HPA axis are one phenomenon read out in different tissues.

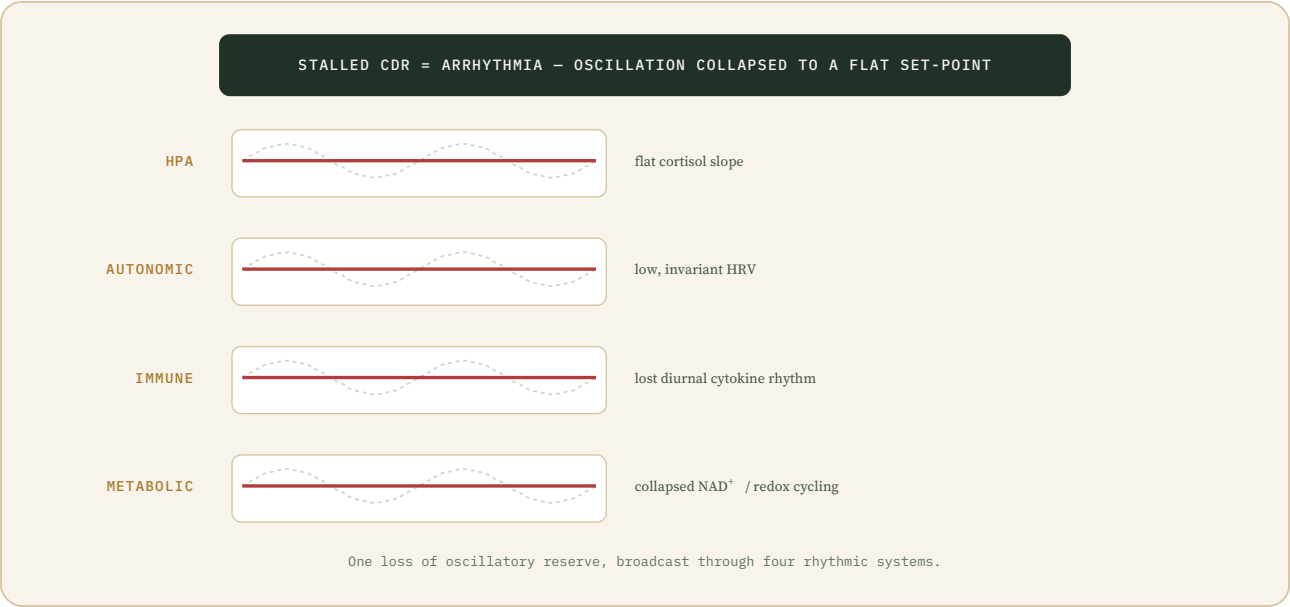

FIGURE 5. One loss of oscillatory reserve, broadcast through four rhythmic systems: HPA (flat cortisol slope), autonomic (low, invariant HRV), immune (lost diurnal cytokine rhythm), and metabolic (collapsed NAD⁺/redox cycling).

PART TWO · THE THESIS

The brain conducts — and VIP is the coupling peptide

The brain broadcasts timing on three channels — the SCN's light-set phase signal, the hypothalamic neuroendocrine pulses, and the brainstem's autonomic oscillation. In the closed gate these generators flatten, functionally and sometimes structurally.

SCN coupling

VIP/VPAC2 is the peptide that phase-locks the SCN's 20,000 oscillators. Without it, neurons desynchronize and amplitude falls.

Pulsatility is signal

GnRH lesson: pulses stimulate, constancy desensitizes. GR transcription is digital — pattern, not mean, carries information.

VIP, two roles

The peripheral resolution / all-clear signal IS the central clock-coupler. Low VIP = a master clock that has lost its coupling peptide.

Clinical corollary. VIP should be delivered gated, pulsatile, and circadian-weighted — not flat QID — once it is understood as a clock-coupling signal as well as a resolution signal.

09 · LABORATORY TRACKING

Biomarkers of CDR / ISRmt progression

The panel reads the trail at three depths: ISRmt-native mitokines report the switch directly; metabolic/mitochondrial assays report its energetic consequences; neuroimmune and oxidative markers report its inflammatory ones. They change in a staggered order toward CDR3.

Biomarker	Tier	Active CDR1/2	Recovery → CDR3
GDF15 · FGF21	ISRmt-native	Elevated — sustained ATF4	Normalizing; transient challenge-rises
Lactate : pyruvate	Metabolic	>20:1 — functional mito arrest	<15:1 — aerobic metabolism resumes
Urinary organic acids	Metabolic	Succinate/fumarate spike (SDH/CxII)	Return to mid-reference
Long-chain acylcarnitines	Metabolic	Elevated — shuttle stalled	Baseline — clean FAO
Histamine · N-methylhist.	Neuroimmune	Elevated — active degranulation	Lower third of range

Biomarker	Tier	Active CDR1/2	Recovery → CDR3
Chromogranin A (+ HRV)	Autonomic	CgA high / HRV low	CgA ↓ / HRV ↑
hs-CRP · IL-6	Neuroimmune	hs-CRP >2.0; IL-6 high	hs-CRP <1.0; IL-6 ~baseline
8-OHdG · cf-mtDNA	Oxidative	Markedly elevated	Measurable drop

Caveats

L:P is preanalytically sensitive (cold, deproteinized draw); CgA is nonspecific (pair with HRV/metanephrines); cf-mtDNA is research-grade — track trend, not absolute.

PART THREE · THE INSTRUMENTS

The Amplitude Biomarker Panel & the ORI

Measure amplitude, slope, and variability — not means. A normal mean cortisol with a flat slope, or a normal heart rate with low RMSSD, is a failed oscillator wearing a normal average, and predicts incomplete CDR3.

Axis	Dynamic metric (not the level)	Stalled / flat	Restored / rhythmic
Neuroendocrine	CAR magnitude; diurnal slope (DUTCH)	Blunted CAR; flat slope; GR resistance	Robust CAR; steep slope
Autonomic	RMSSD; day–night HRV amplitude	Low, invariant; no nocturnal vagal rise	High; restored nocturnal dominance
Circadian	Rest–activity IS/IV/RA; temp amplitude	Damped; low IS, high IV, low RA	Strong amplitude; high IS, high RA
Immune	Diurnal cytokine rhythm (IL-6 AM peak)	Lost variation; tonic inflammation	Restored diurnal rhythm
Cellular / metabolic	Clock-gene amplitude; NAD^+; mitokine diurnal	Damped; collapsed NAD^+; tonic GDF15	Restored amplitude; cycling NAD^+

Oscillatory Reserve Index (ORI). A weighted composite of these dynamic metrics — intended to do for rhythm what the Readiness-to-Heal Index does for level, gating the move to fortification.

BIOENERGETIC CONFIRMATION

Seahorse: spare respiratory capacity as the CDR2 reserve readout

Of the Mito Stress Test outputs, spare respiratory capacity (SRC = maximal − basal) is the most CDR2-relevant parameter — the bioenergetic literal of the "drained battery." It reads the consequence of the stalled ISRmt, not the switch itself, and carries the same mosaic caveat as any blood marker.

Parameter	CDR2 signature
Spare respiratory capacity	Markedly ↓ / negative — the headline
Maximal respiration	Suppressed (low ΔΨm, fragmented net)
ATP-linked OCR	Reduced — OXPHOS → glycolysis
Proton leak	Often ↑ (mPTP, Cx I/III leak)
Basal OCR	The trap — may read normal/high
ECAR / glycolytic flux	Elevated — map shifts to stressed

READ WITH CARE **Mosaic / sample:** PBMCs average across CDR1/2/3 — but M1→M2 is trackable
CDR1 vs CDR2: both suppress OXPHOS — needs mitokines + lineage
Clock-gated: PGC-1α-rhythmic — sample at two times for amplitude

> **Position SRC as the bioenergetic complement to the ISRmt-native mitokines.** GDF15/FGF21 report the switch; Seahorse reports what the switch did to the engine. Rising SRC + receding mitokines = genuine CDR3 progression.

11 · THE FOUR PHENOTYPES

Four points at which the same recovery stalls

A CDR1-Dominant

"Still Alarmed"

MMP-9 ↑ · GDF15 normal/mild

Worse at exposure, better away; electric, reactive. **Phase-5:** finish clearing alarm + limbic retraining (EMDR). A2: limbically conditioned.

B CDR2-Mitochondrial

"Stuck Engine"

GDF15 >1800 · FGF21 ↑ · immune intact

Flat, non-fluctuating exhaustion; PEM. **Phase-5:** deep mito restoration (CoQ10, NAD^+ , carnitine, ribose), methylene blue, strict pacing.

C CDR2-Immune

"Worn-Out Defender"

GDF15/FGF21 ↑ · CD3/CD4/NK ↓ · viral

Sore throat, night sweats, neuropathic pain. **Phase-5:** rebuild engine AND reconstitute immunity + antiviral — both or plateau.

D CDR3-Blocked

"Closed Gate"

VIP <20 · α-MSH <35 · RMSSD <20 ms

Engine ready, can't receive the all-clear; "glass wall," antidepressant-resistant. **Phase-5:** parasympathetic rehab + gated VIP.

10–11 · THE PROTOCOL

The five-phase gated arc — resolve before fortify

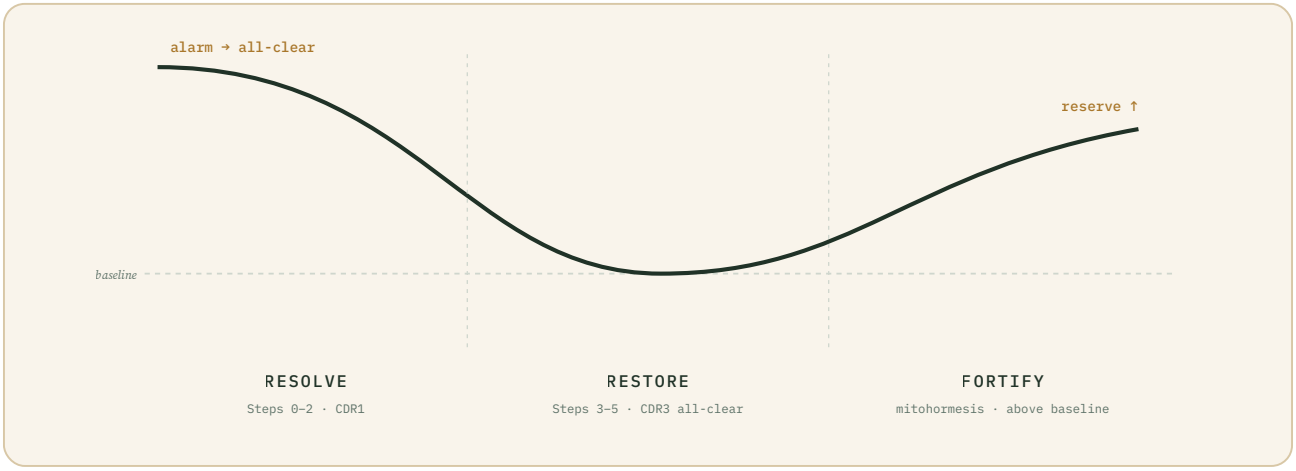

FIGURE 6. The therapeutic arc. Resolve and Restore return the system to baseline — the all-clear. Fortify applies dosed, recoverable stress to raise the baseline.

The ordered all-clear is operationalized as five gated phases. Phases 1–3 are CDR1 work; Phase 4 is CDR2; Phase 5 is CDR3, matched to phenotype. Each phase must clear its exit gate before the next begins.

1	2	3	4	5
Silence the Alarm	**Clear Infections**	**Heal the Gut**	**Rebuild the Engine**	**The Return**
CDR1 · danger	CDR1 · triggers	CDR1 · gut load	CDR2 · siege	CDR3 · matched

> **Reversing or skipping steps predicts failure.** Tolerogenic safety signals over an unresolved infection blunt a needed defense; mitochondrial/hormetic demand before ISRmt resolves asks for output the cell cannot yet produce.

PHASES 1–3 · CDR1

Removing danger, triggers, and gut-derived load

#	Focus	Core interventions	Exit gate
1	Silence the Alarm	Remediation / relocation (confirmed clean); binders (CSM, charcoal, bentonite); glutathione (NAC, PC); neuroinflammation & deep-sleep support	Environment confirmed safe; biotoxin markers improving; symptoms less place-tied

#	Focus	Core interventions	Exit gate
2	Clear Hidden Infections	MARCoNS biofilm decolonized; tick-borne paced + binder-supported; reactivated viruses (EBV/CMV/HHV-6); SIBO & fungal overgrowth	MARCoNS culture negative; infections under treatment; reactions managed
3	Heal the Gut, Rebuild Nutrition	Barrier repair (L-glutamine, zinc-carnosine, colostrum); food triggers; low-mycotoxin diet; microbiome; replete Mg, B, D, CoQ10	Permeability improving; food reactions settling; nutrient deficits corrected

> **MARCoNS exotoxins degrade α-MSH directly** — clearing the nidus in Phase 2 is prerequisite to restoring the all-safe signal later.

PHASE 4 · CDR2

Rebuild the engine — exit the siege

Phase 4 is anabolic and energy-costly; it cannot run until the alarm is quiet. Three workstreams run together, gated by an explicit biomarker exit.

Mitochondrial cofactors

CoQ10 / ubiquinol · NAD^+ · L-carnitine · riboflavin · ALA · D-ribose

Hormonal restoration

Cortisol rhythm · free-T3 · DHEA-S · sex hormones · vitamin D

Autonomic rehab

Resonance breathing · HRV biofeedback · graded exercise · vagal toning

EXIT GATE — PHASE 4 → PHASE 5 GDF15 / FGF21 ↓ MMP-9 normal TGF-β1 approaching ref VEGF restored VCS passed hormones restored HRV shows vagal capacity

08 · INTERVENTION

The therapeutic matrix — three fronts + a resolution arm

Because the pathology converges on one switch, intervention has two levers: lower the upstream drive that keeps eIF2α phosphorylated (three columns), and restore the resolution signal that lets it dephosphorylate (the resolution arm).

Mitochondrial & threshold	Immune & mast-cell	Nerve desensitization & resolution
Raise the energetic floor LOWER UPSTREAM DRIVE	**Prevent the inflammatory leak** LOWER UPSTREAM DRIVE	**Intercept & resolve** SECOND LEVER
Riboflavin (B2) 400 mg/d	**Quercetin** 500–1000 mg/d	**CGRP mAbs / gepants** preventive / acute
CoQ10 150–300 mg/d	**Luteolin** 100–200 mg/d	**Non-invasive vagus** nVNS
Magnesium 400–600 mg/d	**Omega-3 EPA/DHA** 2–4 g/d	**Buccal / sublingual VIP** resolution arm
Methylene Blue 25–50 mg/d	**Compounded NSAID** transdermal	**Compounded capsaicin** 0.025–0.1%

> **The two levers.** The three columns lower the OMA1–DELE1–HRI stimulus, remove inflammatory fuel, and quiet the signal in flight; the resolution arm (VIP at VPAC, supported by vagal tone) works the other lever — to release the cell from arrested CDR1/2 and permit CDR3.

THE RESOLUTION ARM

Why buccal / sublingual VIP — and why not intranasal

1

Exploit the asymmetry

VIP is near-inert at PAC1 and acts at VPAC1/2 — the anti-inflammatory, Treg-favouring, autonomic-settling receptors. It engages the stand-down arm of the same axis PACAP uses to escalate — a pro-CDR3 signal without the migrainogenic PAC1 drive.

2

Kinetics favour transmucosal

VIP's plasma half-life is minutes; buccal/sublingual gives slower, sustained transmucosal absorption — better for tonic VPAC engagement than a single pulse.

3

Route is mechanistically loaded

The nasal mucosa is densely trigeminally innervated and TRP-rich; in a patient whose pathology IS trigeminal sensitization, intranasal delivery risks stimulating the very afferents driving the danger state. The buccal/sublingual field absorbs while largely sparing that territory.

DELIVERY AS A DIFFERENTIATION POINT

The intranasal-VIP method sits within an existing patent estate (US 9,770,170 B2). A buccal / sublingual route is therefore of specific interest — clinically (mucosal absorption, acceptability) and as a deliberately distinct delivery construct from the intranasal claim. Make any route decision with current freedom-to-operate guidance in hand.

Published Shoemaker protocol. Intranasal 50 µg per metered spray QID (short half-life drives frequent dosing); SubQ ~50 µg AM/PM also used. Early transient flare usually signals an unmet prerequisite, not VIP intolerance.

12 · FORTIFICATION

Mitohormesis — building reserve above baseline

Once the all-clear is issued, the system is fortified by the opposite of avoidance. Transient, low-dose ROS from exercise or caloric restriction signals to the nucleus, converging on two physically-interacting programs.

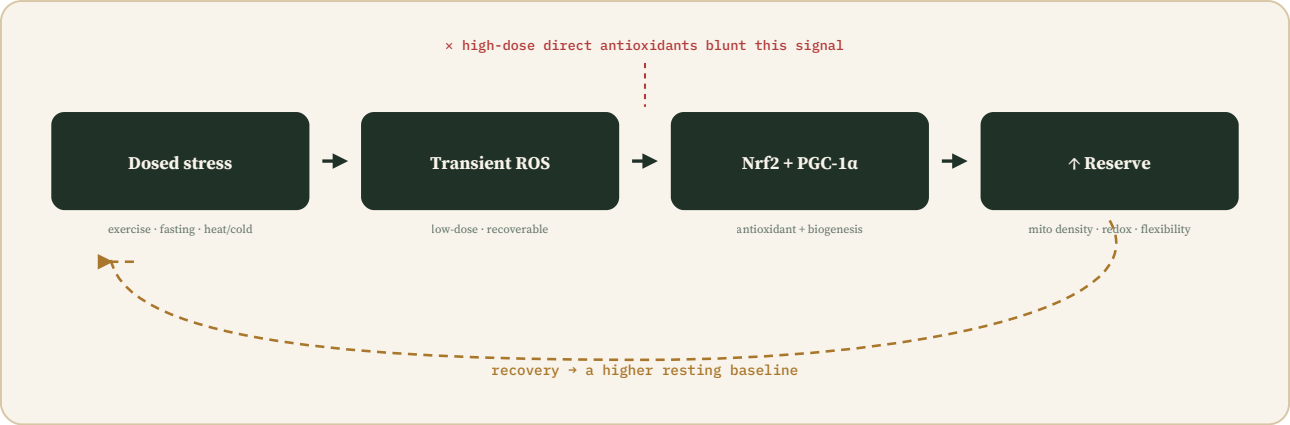

FIGURE 7. The mitohormesis loop. The adaptive signal is the transient ROS — which is why mistimed, high-dose direct antioxidants work against the goal. Inducible Nrf2 capacity is what to build.

Do not blunt the signal

The adaptive cue is the transient ROS itself — large-dose exogenous antioxidants around training abolish the benefit. Build inducible Nrf2 capacity, not chronic antioxidant blockade.

Do not stress an unresolved system

Hormetic load over an active alarm or a depleted battery is simply another threat. Fortification follows resolution; it never substitutes for it.

Read both at every visit. Where is the alarm (residual danger, stalled stage) and what is the reserve (capacity to recover and resist). Declaring victory when inflammation falls but reserve is absent leaves a fragile, relapse-prone state.

PART THREE · §9

The phase-gated zeitgeber table

Chronobiological interventions are gated by the same rule — *resolve before fortify*. Zero-load entrainers first; pulsatile endocrine and central re-coupling as the conductor comes online; metabolic/hormetic loads only once the engine can support oscillation.

Phase	Chronobiological interventions	Amplitude markers to watch
1 · CDR1	Light discipline (AM light / PM dark); SWS protection; social-rhythm regularity; resonance breathing / HRV / taVNS	CAR/slope steepening; nocturnal HRV rising; sleep regularity
2 · CDR1	Maintain entrainers; begin gated, circadian-weighted VIP only once MARCoNS/markers permit	Stable/improving rhythm under treatment load
3 · CDR1	Consistent meal timing (ahead of restriction); gentle NAD^+ precursor ramp; substrate (Mg, B, omega-3)	NAD^+ trend; emerging diurnal variation; slope/HRV gains
4 · CDR2	Timed graded exercise (zone-2→intervals); TRE; mild thermal; pulsatile endocrine; full NAD^+; Tier-D if central damage suspected	SRC ↑; HRV amplitude ↑; mitokines ↓ & re-gaining diurnal variation; ORI climbing
5 · CDR3	Phenotype-matched amplitude work: closed gate → gated VIP as SCN re-coupler + neurotrophic tier; mitohormetic fortification	ORI as gating composite; restored CAR/slope, day–night HRV, RA, temp amplitude

PART FOUR

Phenotype D — The Closed Gate

The drivers are handled — exposure removed, binders run, infections addressed, engine no longer frankly depleted — yet the patient does not recover. The biology has cleared the threat but cannot act on the signal that the threat is over. Three molecular latches, plus an autonomic system still broadcasting danger, hold restoration out of reach.

PHENOTYPE D · THE CLOSED GATE

A failure of the Phase 2 → Phase 3 hand-off

THREE MOLECULAR LATCHES **eATP / P2X7** — the purinergic gatekeeper
eIF2α-P — the ISR translational brake **VIP↓ · α-MSH↓** — the missing all-safe signal

The laboratory signature — no single marker; the pattern

- **All-safe neuropeptides.** VIP low; α-MSH low — the defining pair, anchored to D.
- **ISRmt surrogates.** GDF15 / FGF21 elevated out of proportion to a now-quiet exposure.
- **Residual inflammation.** MMP-9, C4a, TGF-β1 trending down yet symptoms persist — the discordance that defines D.
- **Autonomic.** Low resting HRV; blunted parasympathetic reactivity; poor recovery slope.

PHENOTYPE D · STRATEGY

Two levers open the same gate

The gate is held by both a brake and a missing signal, so it opens to two complementary levers. Relieve the ISR while the all-safe channel is silent and the cell has permission but no instruction; supply the peptide while the brake is clamped and the instruction reaches a cell that cannot translate it.

Axis 1 — Quiet danger · relieve the ISR

Lower what still drives the stress kinases — residual exposure, oxidative load, purinergic signalling, microglial activation — and tip eIF2α back toward dephosphorylation so translation (and 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 parasympathetic tone that carries the same message from the top down.

Applied in sequence, on a foundation of confirmed safety → the gate opens, Phase 3 resumes.

THE EIF2A SWITCH

Where the agents act

Most deployable tools work by lowering the kinase drive rather than directly forcing the phosphatase. Agents that prolong eIF2α-P are protective in other diseases but are the wrong direction here.

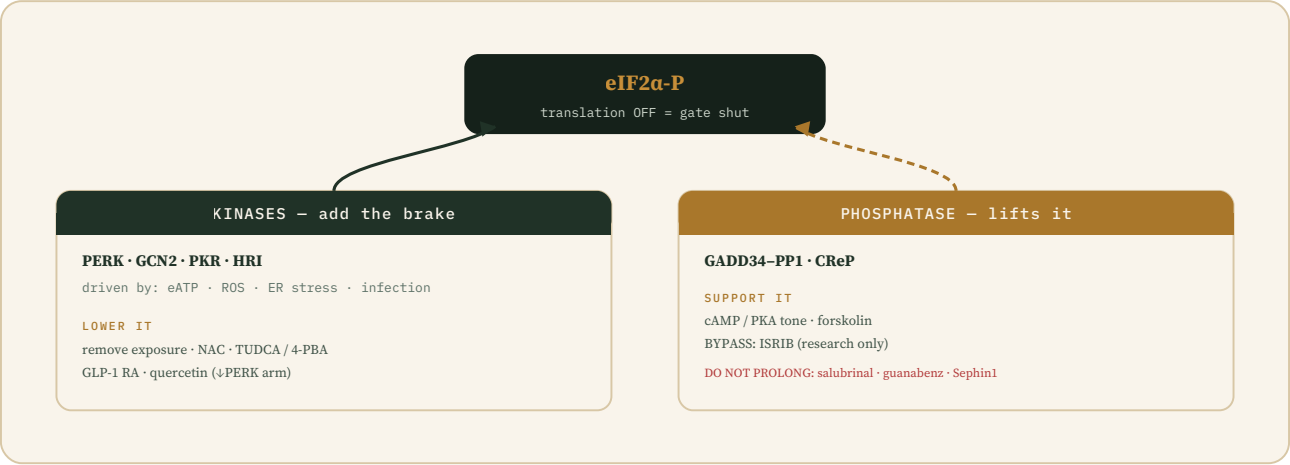

FIGURE 8. Kinases (PERK, GCN2, PKR, HRI) add the brake; the GADD34–PP1 / CReP phosphatase lifts it. Deployable tools mostly lower kinase drive (remove exposure, NAC, TUDCA/4-PBA, GLP-1 RA, quercetin) or support the phosphatase (cAMP/PKA, forskolin). Do not use agents that prolong eIF2α-P (salubrinal, guanabenz, Sephin1).

THE GATE YOU MUST EARN

Prerequisites — before any gate-opening agent

You cannot open the gate while the danger is real. The most common cause of a VIP "non-response" is an unmet prerequisite, not an ineffective drug. This checklist 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	An accurate alarm should not be silenced; opening into exposure reliably flares
Binder / clearance done	Adequate sequestration; symptoms stabilized	Circulating biotoxin keeps kinase drive high — the ISR re-clamps
Source control	MARCoNS / occult infection addressed; sinus & gut handled	A persistent nidus re-activates P2X7 and the stress kinases
Inflammatory markers ↓	MMP-9, C4a, TGF-β1 falling on serial draws	Direction matters more than absolute value — drivers must be receding
Mitochondrial floor	No frank Phenotype B depletion; cofactors repleted	Restoration is anabolic; an empty engine can't execute the repair

> **Read the discordance as the green light.** Drivers controlled and falling, yet VIP/α-MSH still low and ISR surrogates high — that mismatch is the signature of a signalling problem, not an active threat.

AXIS 1 · AGENTS

Quieting the danger & relieving the ISR

Agent	Lever	Dosing	Key cautions	Ev.
Low-dose naltrexone	Microglia / TLR4	1.5 → 3–4.5 mg qHS	Vivid dreams; opioid agonists contraindicated	B
GLP-1 RA	PERK arm / neuroinflammation	Low, slow titration	GI; lean-mass loss in low-reserve; MTC/MEN2	B
Forskolin	cAMP / PKA → phosphatase	~25–50 mg/d (10% extract)	Hypotension (additive w/ VIP); gastric acid	C
Quercetin	ER stress / mast cell	500 mg 1–2×/d	CYP3A4 / P-gp inhibition; high-dose renal	C

Agent	Lever	Dosing	Key cautions	Ev.
NAC	Redox / glutathione	600–1200 mg 1–2×/d	GI; rare bronchospasm	B
TUDCA / 4-PBA	ER chaperone	TUDCA 250–500 mg 1–2×/d	Loose stools; 4-PBA sodium / taste	C

Avoid. Salubrinal, guanabenz, Sephin1/raphin1 prolong eIF2α-P by inhibiting GADD34 — the opposite of the Phenotype D goal. In practice the cleanest way to lift the brake is to stop pressing it.

AXIS 2 · AGENTS

Restoring the neuroendocrine all-safe signal

Agent	Lever	Dosing	Key cautions / role	Ev.
VIP	All-safe (keystone, LAST)	IN 50 µg QID or LPT 200 mcg TID	Hypotension/flush; malignancy caution; the final step	B
KPV	α-MSH proxy	~200–500 µg/d oral	↓IKK→NF-κB; barrier repair; limited human data	C
Oxytocin	Safety / vagal	IN ~10–100 IU	↓NF-κB/cytokines; ↑vagal; pregnancy, hyponatremia	C
Thymosin α-1	Immune retraining	~1.6 mg SubQ 2×/wk	Rebalances Treg set-point; well tolerated	C
PACAP	VIP cousin — caution	Experimental	Shares VPAC/PAC1; migraine & stress-axis trigger	D

Sequencing within Axis 2. KPV and oxytocin are gentle primers introduced as Axis 1 quiets the danger drive; VIP is the keystone, reserved for last. Pair the peptides with autonomic safety work (HRV resonance breathing, taVNS) — a body whose afferent tone still reads danger keeps re-closing the gate. BPC-157 and Semax/Selank belong to the rebuild that follows, not the opening.

08 · THE ROADMAP

A sequenced, gated protocol to open the gate

The agents only work in order. Each stage has an entry condition and an exit criterion; VIP is reached only when the stages beneath it are secure. A flare is information — step back a stage, re-secure it, and re-advance.

0 — **Confirm prerequisites** THE HARD GATE

Re-hunt for a missed source before anything else.

EXIT GATE: Prerequisite checklist met (see above)

1 — **Quiet danger + autonomic base** AXIS 1 FOUNDATION

LDN titration · NAC/quercetin ±TUDCA · HRV resonance/taVNS · sleep/light · ±low-dose GLP-1.

EXIT GATE: danger drive falling; autonomic base in place

2 — **Relieve ISR + prime all-safe** AXIS 1 → AXIS 2

Add KPV & intranasal oxytocin · ±forskolin (cAMP) · thymosin α-1 if immune retraining indicated.

EXIT GATE: primers tolerated; markers stable/improving

3 — **Open the gate — VIP** AXIS 2 KEYSTONE

Introduce VIP only now, on the secured foundation · IN 50 µg QID (or SubQ) · start low if BP low.

EXIT GATE: VIP tolerated; all-safe pair rising

4 — **Consolidate the rebuild** PHASE 5 / FORTIFY

NAD^+ · CoQ10/PQQ · urolithin A · creatine · cofactors · taper scaffolding as VIP/α-MSH/HRV normalize.

EXIT GATE: rhythm + reserve restored; ORI climbing

Entry to the whole sequence. Phenotype D confirmed · drivers controlled and falling · VIP/α-MSH low with persistent symptoms.

10 · EVIDENCE, SAFETY & SOURCING

Monitoring & contraindications

Track the markers that defined the phenotype, on a sensible cadence — direction of travel matters more than any single value.

MONITOR

- VIP / α-MSH — the defining pair
- GDF15 / FGF21 — ISR surrogates
- MMP-9 / C4a / TGF-β1 — drivers
- HRV — autonomic recovery
- BP — VIP & forskolin (additive hypotension)
- Metabolic & GI tolerance — GLP-1
- Sleep — LDN

CONTRAINDICATIONS TO HOLD IN VIEW

- Opioid agonists × LDN
- Active malignancy × VIP
- MTC / MEN2 × GLP-1 RA
- Pregnancy × oxytocin & several peptides
- Additive hypotension: VIP + forskolin + antihypertensives
- Migraine-prone × PACAP

Off-label, compounded, and honestly graded

Every peptide here is used off-label and most are compounded — source from reputable pharmacies with potency and sterility documentation; research-only material is not for human use. Only VIP (CIRS cohorts) and LDN/GLP-1 (adjacent indications) rise to good human data (grade B); KPV, oxytocin, forskolin, quercetin, the chaperones and adjacent peptides rest largely on preclinical and mechanistic support. Grades are deliberately conservative.

SYNTHESIS

One switch, sequenced — and opened last

CIRS is a validated special case of the CDR/ISRmt framework: five pathways converge on one mitochondrial checkpoint, governed by a single switch whose failure to terminate is the lesion. Recovery is sequenced and phenotype-matched; read chronobiologically, CDR3 is the resumption of rhythm, confirmed by amplitude, not means.

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 — a clinical synthesis, not a guideline, and not individualised medical advice.