CLINICAL LEARNING GUIDE

VIP

Vasoactive Intestinal Peptide | 28-Amino-Acid Endogenous Neuropeptide | Immunomodulatory / Neuroprotective

Mechanisms, Evidence, and Clinical Applications

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SECTION 1 · PROFILE OF THE PEPTIDE

Overview

Vasoactive Intestinal Peptide (VIP) is a 28-amino-acid neuropeptide discovered in 1970 and — unlike most of the peptides in this series — it is endogenous, a natural human signaling molecule rather than a synthetic analog. It is widely distributed throughout the central and peripheral nervous systems and is, by volume, among the most abundant neuropeptides in the brain. It signals through two Class B G-protein-coupled receptors, VPAC1 and VPAC2, found on immune cells, neurons, and tissues of the lung, liver, gut, and pancreas.

VIP is genuinely pleiotropic. It is a potent vasodilator and bronchodilator (50–100× more potent than acetylcholine as a vasodilator), a broad anti-inflammatory and immunomodulatory agent, and a neuroprotectant that quiets activated microglia. Its most distinctive property is dual-pathway immune modulation: it suppresses inflammatory cytokines while simultaneously promoting immune tolerance (regulatory T cells, tolerogenic dendritic cells, a Th1→Th2 shift, and reduced pathogenic Th17) — addressing both the inflammatory and the autoimmune sides of disease at once, which few single agents do. A practical constraint shapes everything: VIP's plasma half-life is only ~1–2 minutes (rapid peptidase degradation), which limits systemic use and is the reason it is delivered intranasally.

VIP occupies a hopeful but evidence-limited position the practitioner must hold in full. Its mechanism is rich and well-characterized, it has one positive (if small and open-label) human trial in pulmonary hypertension, strong preclinical data across autoimmune and inflammatory disease, and open-label clinical use in chronic inflammatory response syndrome (CIRS/mold illness). At the same time, there are no large randomized controlled trials for essentially any indication, it is not FDA-approved (used off-label as a compounded preparation), and its VPAC receptors' presence on some tumors mandates malignancy screening. A compelling, pleiotropic mechanism with mostly preclinical and open-label human support is not the same as RCT-validated therapy — and conveying both is the central task.

Peptide Profile

Property	Detail
Name / identity	Vasoactive Intestinal Peptide; 28-amino-acid endogenous neuropeptide (discovered 1970)

Property	Detail
Distribution	Widely distributed in CNS and PNS; among the most abundant neuropeptides in the brain
Receptors	VPAC1 and VPAC2 (Class B GPCRs) on immune cells, CNS, lung, liver, gut, pancreas
Core actions	Vasodilation/bronchodilation; anti-inflammatory + immunomodulatory (dual-pathway); neuroprotection (microglial deactivation)
Signaling	G_s → adenylyl cyclase → cAMP → PKA → NF-κB inhibition; also p38 MAPK/ERK inhibition, PLC/Ca^{2+}, PI3K
Half-life	~1–2 minutes (rapid peptidase degradation) — limits systemic use
Route	Intranasal spray (primary); inhalation (pulmonary HTN trial)
Strongest human data	Pulmonary hypertension — open-label, n=8 (Petkov 2003)
Other human use	Open-label CIRS/mold (Shoemaker protocol); most other indications preclinical
Cautions	VPAC receptors on some tumors (screen for malignancy); vasodilatory hypotension
Regulatory	NOT FDA-approved; off-label compounded; not on 503A category-1 list

Where VIP Sits

VIP closes this neuroprotection series as something of an outlier and a synthesis. It is the only endogenous human peptide of the group — not a designed analog — and its center of gravity is immune modulation rather than a single neurologic target, though its neuroprotective (microglial-quieting, neurotrophic) and CNS roles place it squarely in the neuroprotection conversation. Where the synthetic peptides in this series tend to push one or two pathways, VIP is broadly pleiotropic and, distinctively, rebalances the immune system in both directions at once. VIP is best thought of as an immune modulator — not a booster or a suppressor — with real promise across chronic inflammatory and autoimmune conditions, neuroinflammation, CIRS/mold illness, and even circadian regulation, while being candid that its human evidence base is thin (one small trial plus open-label experience) and that large controlled trials are still needed.

> **⚠ VIP is NOT FDA-approved — it is used off-label as a compounded preparation and is not on the 503A category-1 list. The strongest human data are a single small open-label trial in pulmonary hypertension (n=8); most other evidence is preclinical or open-label (CIRS). There are NO large randomized controlled trials for essentially any indication. SCREEN FOR ACTIVE MALIGNANCY before use — VPAC receptors are overexpressed on some tumors. VIP is a potent vasodilator: watch for light-headedness and transient hypotension, and use caution with antihypertensives. Avoid in pregnancy (insufficient data). The very short half-life (~1–2 min) is why it is given intranasally. Full informed consent is essential.**

SECTION 2 · MODES OF ACTION AND MECHANISMS

VIP works through two receptors (VPAC1 and VPAC2) that funnel into a common cAMP/PKA signaling hub, from which its anti-inflammatory, immune-tolerizing, neuroprotective, and

vasodilatory effects radiate. The unifying idea is rebalancing: VIP simultaneously turns down inflammatory signaling and turns up tolerance, which is what distinguishes it from agents that simply block one cytokine or broadly suppress immunity. Most mechanistic data are preclinical and in-vitro, complemented by the small human and open-label clinical work.

Receptor Signaling: VPAC1 and VPAC2

VPAC1 is widely distributed (immune cells, CNS, liver, lung/airway, gut). It couples to G_s → adenylyl cyclase → cAMP → PKA, and through PKA it inhibits NF-κB — the central driver of pro-inflammatory gene transcription — mediating much of VIP's anti-inflammatory effect. VPAC2 is enriched in immune tissue and the pancreas (also lung, liver, gut); it stimulates glucose-dependent insulin secretion (via PI3K), suppresses Th1/Th17 function, and promotes a Th2 shift with expansion of regulatory T cells. Downstream of both receptors, the cAMP/PKA axis blocks the IKK–IκB–NF-κB cascade, inhibits p38 MAPK and ERK, activates PLC/Ca^{2+} signaling, and (via VPAC2/PI3K, with FoxM1) can promote pancreatic β-cell proliferation.

Immune Modulation: Anti-Inflammatory + Immune Tolerance

VIP's signature is acting on both arms of immune dysregulation. On the inflammatory side it suppresses TNF-α, IL-1β, and IL-6 while upregulating the anti-inflammatory mediators IL-10 and IL-1Ra, and it inhibits microglial activation. On the tolerance side it generates $CD4^+CD25^+$ regulatory T cells (Treg) in vivo, induces tolerogenic dendritic cells, shifts the Th1→Th2 balance, and reduces the pathogenic Th17 profile (raising the Treg/Th17 ratio). This combination — damping inflammation while actively building tolerance — is what lets VIP address both the inflammatory and the autoimmune components of disease, a dual reach that single-cytokine blockers and broad immunosuppressants do not have (see the note below).

Neuroprotection

VIP's neuroprotection is largely an extension of its immune effect in the CNS: it inhibits microglial activation and the microglial production of inducible nitric oxide (iNOS), IL-1β, and TNF-α, reducing neuroinflammatory injury. It also promotes neuronal survival through the release of activity-dependent neurotrophic factor (ADNF). A potency note from the literature: the analog stearyl-Nle^{17}-VIP is reported to be ~100-fold more potent for neuroprotection in vitro — an illustration of how the scaffold can be tuned, though it is a research analog rather than VIP itself.

Vasodilation & Bronchodilation

VIP is a remarkably potent vasodilator — 50–100× more potent than acetylcholine — relaxing vascular and bronchial smooth muscle through VPAC1/VPAC2 and cAMP. It inhibits platelet activation and vascular smooth-muscle-cell proliferation (relevant to pulmonary hypertension) and relaxes airway smooth muscle (relevant to asthma and COPD). This vasodilatory power is also the source of its main side effect: light-headedness and transient hypotension.

> **Key mechanistic point: VIP is an endogenous 28-aa neuropeptide acting through VPAC1/VPAC2 → cAMP/PKA, which inhibits NF-κB (and p38 MAPK/ERK). It is a DUAL-PATHWAY immune modulator — suppressing TNF-α/IL-1β/IL-6 and raising IL-10/IL-1Ra (anti-inflammatory) WHILE generating Tregs, tolerogenic dendritic cells, and a Th1→Th2 shift with reduced Th17 (immune tolerance). It is neuroprotective (microglial deactivation, iNOS/TNF-α suppression, ADNF release) and a potent vasodilator/bronchodilator (50–100× acetylcholine). The mechanism is rich and human-relevant, but most of the data are preclinical, and the ~1–2-minute half-life dictates intranasal delivery.**

A Note on Modulation vs Suppression

The most important conceptual point about VIP is that it is an immune modulator, not an immune booster or an immune suppressant. A TNF inhibitor blocks a single cytokine; a corticosteroid broadly suppresses immunity (with the infection risk that entails). VIP instead rebalances: it lowers inflammatory signaling at the same time as it strengthens the tolerance machinery (Treg, tolerogenic dendritic cells), nudging a dysregulated immune system back toward equilibrium rather than simply turning it down. This is why VIP can, in principle, help autoimmune conditions (where tolerance has failed) and inflammatory conditions (where signaling is excessive) through the same mechanism, and why its infection-risk profile is described as low relative to TNF inhibitors or steroids. The same modulatory logic underlies its use in CIRS/mold illness and its appeal in neuroinflammation. The caveat: "modulation" is a mechanistic description supported largely by preclinical data, and the theoretical additive risk with other immunosuppressants — and the malignancy caution from VPAC expression on tumors — still apply.

SECTION 3 · POINTS OF CLINICAL RELEVANCE

- **The defining tension.** A rich, pleiotropic mechanism and one small positive human trial — but no large RCTs.

VIP's mechanism is well characterized and human-relevant, it has a positive (if small, n=8, open-label) human trial in pulmonary hypertension, strong preclinical autoimmune/inflammatory data, and open-label CIRS use. But there are no large randomized controlled trials for essentially any indication, and it is not FDA-approved. A compelling mechanism plus preclinical and open-label support is not RCT-validated therapy, and that must be disclosed.

- **An endogenous peptide — the brain's most abundant.** A different kind of agent from the rest of this series.

Unlike the synthetic analogs elsewhere in this series, VIP is a natural human neuropeptide, widely distributed and abundant in the CNS. Using it is less about introducing a novel molecule and more about supplementing or modulating an endogenous signaling system — which shapes both its broad effects and its short half-life.

- **A dual-pathway immune modulator.** It addresses inflammation and autoimmunity at once.

VIP suppresses inflammatory cytokines (TNF-α, IL-1β, IL-6) while building tolerance (Tregs, tolerogenic dendritic cells, Th2 shift, reduced Th17). No single conventional agent targets Th1/Th17 suppression plus Treg induction simultaneously — the basis for its appeal in both autoimmune and inflammatory disease, and its "modulator, not suppressor" character.

- **Strongest human data is pulmonary hypertension.** Striking results, but a very small open-label study.

In 8 PPH patients, inhaled VIP improved mean pulmonary artery pressure, cardiac output, pulmonary vascular resistance (~50% reduction), and 6-minute walk distance, with no significant side effects and unchanged systemic BP/HR. The findings are impressive and mechanistically coherent (PPH patients are VIP-deficient with upregulated VPAC receptors) — but n=8 and open-label, needing Phase II/III confirmation.

- **A favorable comparison with conventional immunomodulators.** Treg induction, neuroprotection, low infection risk.

Versus TNF inhibitors (single-cytokine, no Treg induction, no neuroprotection, moderate-high infection risk) and corticosteroids (broad suppression, no autoimmune correction, high infection risk), VIP uniquely combines anti-inflammatory and pro-tolerance effects with neuroprotection and a low infection-risk profile, delivered intranasally. This is a conceptual advantage — tempered by the thin human evidence base.

- **CIRS/mold and circadian applications.** Open-label and case-study experience, respectively.

VIP is used late in the Shoemaker CIRS protocol (after upstream steps) with open-label reports of durable benefit and even restored grey-matter volume. Separately, because VIP is central to the suprachiasmatic (circadian) clock, it is used — on case-study basis only — in the morning to help reset circadian rhythm in jet lag or shift work. Both are promising but not RCT-supported.

- **Short half-life, malignancy caution, no RCTs.** The central limitations, stated plainly.

The ~1–2-minute half-life forces intranasal (or nanomedicine/future) delivery; VPAC receptors on some tumors mandate malignancy screening; the vasodilatory effect can cause hypotension; and the absence of large RCTs keeps VIP investigational. These constraints define responsible use.

SECTION 4 · GENERAL DOSING INSTRUCTIONS AND DELIVERY OPTIONS

VIP is NOT FDA-approved and is used off-label as a compounded preparation; its ~1–2-minute half-life makes intranasal the practical route. SCREEN FOR ACTIVE MALIGNANCY before initiating (VPAC receptors on some tumors). Start low and titrate with blood-pressure monitoring — VIP is a potent vasodilator and can cause light-headedness/hypotension; use caution with antihypertensives. Avoid in pregnancy. Dosing below is from clinical trials, open-label work, and clinical practice — not FDA-approved guidance.

Dosing by Indication

Indication	Route	Dose	Frequency / Duration	Evidence
Pulmonary hypertension	Inhalation	50 mcg × 4 (200 mcg/day)	Daily × 3–6 mo	Clinical trial (n=8)
Inflammatory support	Intranasal	0.2–0.4 mg/day	Daily, divided	Clinical practice
Respiratory	Intranasal	up to 0.4 mg/day	Daily, adjusted	Clinical practice
Neurological	Intranasal	0.2 mg start	Daily, titrated	Clinical practice
CIRS / mold illness	Intranasal	Per Shoemaker protocol	Daily, 18+ mo	Open-label

Formulation & Administration

- Compounded intranasal spray, typically 1–5 mg/mL in saline (so on the order of ~500 mcg per spray); requires a licensed compounding pharmacy meeting USP <797> sterile standards; store refrigerated and protect from light.
- Technique: alternate nostrils with each dose, prime the spray before first use, tilt the head slightly forward, and avoid blowing the nose for ~10 minutes after dosing.
- Titration: start at the lowest effective dose (~0.2 mg/day), assess tolerance, and titrate by clinical response and blood pressure; pulse dosing may reduce any receptor desensitization (theoretical — limited data, and desensitization may not occur).
- Duration varies by indication — roughly 3–6 months for pulmonary hypertension up to 18+ months for CIRS; open-label long-term use has been reported without significant adverse effects.

Practice Approach (Intranasal, Morning-Weighted)

- Intranasal dosing of roughly 200–400 mcg per spray (up to ~500 mcg), commonly 1–2 sprays first thing in the morning and 1–2 sprays later in the morning, titrated to the immune/inflammatory issue and to patient tolerance.
- Generally morning-weighted and not used in the late afternoon/evening — reflecting VIP's circadian role (see below); can be used daily, with durations of ~3–12 months.
- For CIRS/mold, VIP is a late-stage step (Shoemaker steps 10–12), started only after upstream factors are addressed (see Section 6).
- Dosing is patient-specific and response-guided; given the vasodilatory effect, blood-pressure monitoring and a low starting dose are prudent.

Combinations & Emerging Delivery

Reported and investigational combinations are mostly preclinical: VIP plus probiotics (e.g., L. casei) gave superior colitis relief in mice via NF-κB and Nrf2 modulation; VIP nanomedicine (sterically stabilized micelles, "VIP-SSM") protects the peptide from degradation, extends its half-life, and enhances anti-inflammatory effect at lower doses; and lentiviral VIP gene therapy produced sustained immunomodulation and tolerogenic dendritic cells in mice. A separate, important distinction: in CAR-T cancer immunotherapy it is VIP-receptor ANTAGONISM (blocking the pathway), not VIP itself, that reprograms CAR-T cells toward a memory phenotype and enhanced anti-tumor activity — consistent with the caution that VIP signaling can be trophic for some tumors. These approaches are not human-validated; the nanomedicine and gene-therapy routes are the main hopes for overcoming VIP's short half-life.

SECTION 5 · EVIDENCE PROFILE

Clinical & Preclinical Evidence by Domain

Domain / Study	Type	Key Finding
Pulmonary hypertension (Petkov 2003)	Clinical (open-label, n=8)	Inhaled VIP: MPAP 59→46 mmHg, CO 4.7→6.4 L/min, PVR ~−50%, 6-min walk +129 m (all $p<0.01$)
Rheumatoid arthritis (Delgado 2001)	Animal	Collagen-induced arthritis: abrogated joint swelling; prevented cartilage/bone

Domain / Study	Type	Key Finding
		destruction; TNF-α/IL-1β down, IL-10/IL-1Ra up
Treg induction (Delgado 2005)	Animal	Generated $CD4^{+}CD25^{+}$ regulatory T cells in vivo
IBD / colitis (Jayawardena 2017)	Animal (nanomedicine)	VIP-SSM reversed DSS colitis better than free peptide; restored DRA; reduced cytokine mRNA
Neuroprotection (White 2010)	Review / animal	Microglial deactivation; iNOS/IL-1β/TNF-α suppression; ADNF-mediated neuronal survival
CIRS / mold (Shoemaker 2013/2017)	Open-label (n~20)	Intranasal VIP after upstream steps: durable benefit; restored grey-matter nuclear volume
GI / immune reviews (Iwasaki 2019; Martinez 2019)	Review	Tight-junction (ZO-1) regulation; Th17/Treg axis; VPAC physiology
Type 2 diabetes / VPAC2 (Hou 2022)	Review	VPAC2 agonists in development; glucose-dependent insulin secretion, β-cell proliferation

What Can and Cannot Be Confirmed

Can confirm	Cannot confirm
An endogenous 28-aa neuropeptide; VPAC1/VPAC2 → cAMP/PKA signaling	RCT-level efficacy for essentially any indication
Dual-pathway immune modulation (anti-inflammatory + Treg/tolerance)	Whether preclinical autoimmune/IBD benefit translates to humans
Positive open-label human results in pulmonary hypertension (n=8)	Confirmed benefit beyond small/open-label studies (no Phase II/III)
Potent vasodilation/bronchodilation; neuroprotection (microglial)	Human pharmacokinetics for chronic use; optimal dosing
Open-label CIRS experience; favorable short-term safety	Long-term safety; safety in pregnancy; tumor-related risk specifics

Critical Evidence Gaps

- No large randomized controlled trials for any indication; the best human data are open-label (PPH n=8; CIRS n~20).
- Most efficacy data are preclinical (rheumatoid arthritis, IBD, MS, type 1 diabetes, neurodegeneration are animal/in-vitro).
- Very short half-life (~1–2 min) limits delivery; nanomedicine and gene therapy are unproven in humans.
- CIRS/circadian uses rest on open-label and case-study data (some CIRS work is not PubMed-indexed).

- No long-term human safety data; pregnancy safety unknown; tumor-related risk from VPAC expression not fully characterized.

SECTION 6 · CLINICAL CONSIDERATIONS

Regulatory & Legal Status

VIP is not FDA-approved and is not available as a finished pharmaceutical; it is used off-label as a compounded intranasal preparation and is not on the 503A category-1 compounding list. It therefore requires a licensed compounding pharmacy (USP <797> sterile standards) and full informed consent covering its off-label, research-supported status. There is no approved indication in the US.

Safety Profile

VIP's reported adverse effects are largely extensions of its potent vasodilation: light-headedness and transient, dose-dependent hypotension, plus nasal congestion (intranasal route) and rare transient flushing. In the pulmonary-hypertension trial there were no significant adverse effects across 8 patients over six months, with systemic blood pressure and heart rate unchanged. Open-label CIRS use over 18+ months has likewise been reported without significant adverse effects. These are reassuring but small, uncontrolled datasets; long-term controlled safety data do not exist.

Contraindications & Precautions

- Active malignancy (or history of VPAC-expressing tumors): VPAC receptors are overexpressed on some tumors and VIP signaling can be trophic — screen for malignancy before use; this is a contraindication.
- Pregnancy/lactation: insufficient safety data — avoid.
- Symptomatic hypotension or cardiovascular instability: the vasodilatory effect may worsen it — caution.
- Drug interactions: additive hypotension with antihypertensives; theoretical additive immune effect with immunosuppressants (though VIP behaves as a modulator rather than a blanket suppressor).

Monitoring

Reasonable monitoring (extrapolated from the trials, the CIRS protocol, and the peptide's pharmacology): blood pressure at each visit and daily at initiation (no symptomatic hypotension); a pre-treatment workup including CMP, CBC, renal and hepatic function, and inflammatory markers; age-appropriate cancer screening before initiation; VIP serum level at baseline and periodically (reference ~0–89 pg/mL) if available; CRP/ESR at baseline and every 3–6 months; and, for CIRS, TGF-β1 and MMP-9 trended toward normal. Track symptom scores for dose adjustment. No VIP-specific efficacy markers are validated outside these.

Patient Selection, the CIRS Protocol & Practitioner Posture

Ideal candidates are adults with chronic inflammatory conditions refractory to standard therapy, autoimmune conditions with a Th1/Th17 predominance, neuroinflammatory conditions (investigational), or CIRS/mold illness — the last only after the upstream protocol steps. Poor candidates include anyone with active malignancy or a history of VPAC-expressing tumors, symptomatic hypotension or cardiovascular instability, or pregnancy. For CIRS specifically, VIP is a late-stage intervention (Shoemaker steps 10–12): removal from exposure, binders

(cholestyramine/Welchol), and MARCoNS correction come first, and ADH/osmolality, MMP-9, VEGF, C3a/C4a, and TGF-β1 should be controlled before VIP is started. The responsible posture mirrors the evidence: present VIP's rich mechanism and its genuine but limited human data (one small PPH trial plus open-label experience) honestly alongside the absence of large RCTs and its off-label status; screen for malignancy; start low with blood-pressure monitoring; obtain full informed consent; favor the intranasal route; and document indication, dose, response, and biomarkers to help build the evidence base that large trials have not yet provided.

SECTION 7 · A FINAL NOTE

VIP is a fitting close to this neuroprotection series — the one endogenous peptide among the synthetic analogs, and the one whose reach is broadest. It is a 28-amino-acid neuropeptide, abundant in the brain, signaling through VPAC1/VPAC2 and a cAMP/PKA hub to do something few single agents can: rebalance the immune system in both directions at once, suppressing inflammatory cytokines while building tolerance through regulatory T cells and tolerogenic dendritic cells. Layered onto that are genuine neuroprotection (quieting activated microglia, releasing ADNF) and potent vasodilation and bronchodilation. It is an immune modulator, not a booster or a suppressor — the conceptual heart of its appeal across autoimmune, inflammatory, neuroinflammatory, CIRS/mold, and even circadian applications.

And yet the honest accounting holds, as it has throughout this series. VIP's strongest human evidence is a single open-label trial of 8 pulmonary-hypertension patients; the autoimmune and inflammatory data are preclinical; the CIRS and circadian uses are open-label and case-study level. There are no large randomized controlled trials for any indication, it is not FDA-approved, its ~1–2-minute half-life constrains delivery to the intranasal route, and the presence of VPAC receptors on some tumors makes malignancy screening mandatory. A rich, pleiotropic, well-reasoned mechanism with mostly preclinical and open-label human support is promising — but it is not RCT-validated therapy.

For the practitioner, the posture is measured optimism with clear guardrails. VIP's biology is compelling and its early human and open-label signals are encouraging, particularly in the immune-tolerance space where conventional agents fall short. Used thoughtfully — intranasally, morning-weighted, started low with blood-pressure monitoring, only after malignancy screening, with full informed consent about its off-label and largely-preclinical status, and as a late step in the CIRS protocol when that is the indication — it can be a valuable tool. As with every peptide in this series, the most useful contribution a clinician can make is to use it carefully, document outcomes and biomarkers, and help build the controlled human evidence that VIP, like its companions here, still needs.

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