VIP — Basic Review Questions

1. What is VIP, and how does it differ from the other peptides in this series?

Answer: VIP (Vasoactive Intestinal Peptide) is a 28-amino-acid neuropeptide discovered in 1970. Unlike most peptides in this series, it is endogenous — a natural human signaling molecule rather than a synthetic analog — and it is, by volume, among the most abundant neuropeptides in the brain, widely distributed in the central and peripheral nervous systems. 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. It is genuinely pleiotropic — a potent vasodilator and bronchodilator, a broad anti-inflammatory and immunomodulatory agent, and a neuroprotectant — and its defining property is dual-pathway immune modulation (acting on both inflammatory and autoimmune components at once). A key practical constraint is its very short plasma half-life (~1–2 minutes), which is why it is delivered intranasally.

2. What is the central tension a practitioner must understand about VIP?

Answer: VIP has a rich, well-characterized, human-relevant mechanism; one positive (if small, n=8, open-label) human trial in pulmonary hypertension; strong preclinical data across autoimmune and inflammatory disease; and open-label clinical use in CIRS/mold illness; there is real promise, especially in immune tolerance. But there are no large randomized controlled trials for essentially any indication, it is not FDA-approved (used off-label as a compounded preparation), its ~1–2-minute half-life constrains delivery, and the presence of VPAC receptors 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 that gap must be disclosed.

3. How does VIP work — from its receptors through its main effects?

Answer: VIP signals through VPAC1 and VPAC2 receptors that funnel into a common cAMP/PKA hub. VPAC1 (widely distributed, including immune cells and CNS) couples to Gs → adenylyl cyclase → cAMP → PKA, which inhibits NF-κB (the central pro-inflammatory transcription driver), mediating anti-inflammatory effects. VPAC2 (enriched in immune tissue and pancreas) stimulates glucose-dependent insulin secretion, suppresses Th1/Th17, and promotes a Th2 shift with regulatory T-cell expansion. Downstream, 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/FoxM1) can promote β-cell proliferation. On the immune side, VIP suppresses TNF-α, IL-1β, and IL-6 while upregulating IL-10 and IL-1Ra, and it generates Tregs and tolerogenic dendritic cells. It is neuroprotective (inhibiting microglial activation and microglial iNOS/IL-1β/TNF-α, and releasing activity-dependent neurotrophic factor, ADNF) and a potent vasodilator/bronchodilator (50–100× more potent than acetylcholine), relaxing vascular and bronchial smooth muscle via cAMP.

4. What does it mean that VIP is a “modulator, not a booster or suppressor,” and why does that matter?

Answer: This is the conceptual heart of VIP. A TNF inhibitor blocks a single cytokine; a corticosteroid broadly suppresses immunity (with attendant infection risk). VIP instead

rebalances the immune system in both directions at once — it lowers inflammatory signaling (TNF-α, IL-1β, IL-6 down; IL-10, IL-1Ra up) while simultaneously strengthening the tolerance machinery (regulatory T cells, tolerogenic dendritic cells, a Th1→Th2 shift, reduced pathogenic Th17). This dual reach means it can, in principle, help autoimmune conditions (where tolerance has failed) and inflammatory conditions (where signaling is excessive) through the same mechanism — something no single conventional agent does — and it is associated with a low infection-risk profile relative to TNF inhibitors and steroids. The caveat: "modulation" is a mechanistic description supported largely by preclinical data, and the malignancy caution (VPAC receptors on some tumors) and theoretical additive risk with other immunosuppressants still apply.

5. Where is the human evidence strongest, and what does the rest of the evidence base look like?

Answer: The strongest human data are in pulmonary hypertension: Petkov 2003, an open-label trial of 8 PPH patients given inhaled VIP (200 mcg/day) for 3–6 months, showed improved mean pulmonary artery pressure (59→46 mmHg), cardiac output (4.7→6.4 L/min), pulmonary vascular resistance (~50% reduction), and 6-minute walk distance (+129 m), all $p<0.01$, with no significant side effects and unchanged systemic BP/heart rate — mechanistically coherent, since PPH patients are VIP-deficient with upregulated VPAC receptors, but only n=8 and open-label. Beyond that, the evidence is preclinical (rheumatoid arthritis, inflammatory bowel disease, MS, type 1 diabetes, neurodegeneration are animal/in-vitro) or open-label (CIRS/mold illness, via the Shoemaker protocol, with reports of durable benefit and even restored grey-matter volume). There are no large randomized controlled trials for any indication.

6. How is VIP dosed, and what is Dr. Seeds' practice approach (including the circadian use)?

Answer: Because of its ~1–2-minute half-life, VIP is used intranasally (the pulmonary-hypertension trial used inhalation, 50 mcg × 4/day). It is a compounded intranasal spray (typically 1–5 mg/mL in saline, on the order of ~500 mcg per spray), refrigerated and protected from light, with technique points (alternate nostrils, prime, tilt head forward, no nose-blowing for ~10 minutes). Start low (~0.2 mg/day) and titrate by clinical response and blood pressure. Dr. Seeds' practice approach is intranasal ~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 tolerance; it is generally morning-weighted (not late afternoon/evening), can be daily, and runs ~3–12 months. A distinctive use: because VIP is central to the suprachiasmatic nucleus (the master circadian clock), it is used — on a case-study basis only — in the morning or at the intended wake time (e.g., ~400–500 mcg per nostril, one to two early/mid-morning doses) to help reset circadian rhythm in jet lag or shift work. For CIRS, VIP is a late-stage step (Shoemaker steps 10–12).

7. What are the key safety considerations, contraindications, and monitoring?

Answer: VIP's main adverse effects are extensions of its potent vasodilation — light-headedness and transient, dose-dependent hypotension — plus nasal congestion (intranasal) and rare transient flushing; in the PPH trial there were no significant

adverse effects over six months, with BP/HR unchanged. The most important contraindication is active malignancy or a history of VPAC-expressing tumors: VPAC receptors are overexpressed on some tumors and VIP signaling can be trophic, so screen for malignancy before use. Other contraindications/cautions: pregnancy/lactation (insufficient data — avoid), symptomatic hypotension or cardiovascular instability (vasodilation may worsen it), additive hypotension with antihypertensives, and a theoretical additive effect with immunosuppressants (though VIP behaves as a modulator rather than a blanket suppressor). Monitoring: blood pressure (each visit, daily at initiation), a pre-treatment workup (CMP, CBC, renal/hepatic, inflammatory markers) and age-appropriate cancer screening before initiation, VIP serum level (baseline/periodic, reference ~0–89 pg/mL) if available, CRP/ESR every 3–6 months, and — for CIRS — TGF-β1 and MMP-9 trended toward normal, with symptom scores tracked for dose adjustment.

8. What is the appropriate practitioner posture toward VIP?

Answer: Measured optimism with clear guardrails. VIP's biology is compelling and its early human and open-label signals are encouraging, especially in the immune-tolerance space where conventional agents fall short. Ideal candidates are adults with chronic inflammatory conditions refractory to standard therapy, autoimmune conditions with Th1/Th17 predominance, neuroinflammatory conditions (investigational), or CIRS/mold illness (only after the upstream protocol steps); poor candidates include anyone with active malignancy or a VPAC-tumor history, symptomatic hypotension or cardiovascular instability, or pregnancy. For CIRS, VIP is a late-stage intervention (Shoemaker steps 10–12), begun only after exposure removal, binders, MARCoNS correction, and control of ADH/osmolality, MMP-9, VEGF, C3a/C4a, and TGF-β1. The responsible posture is to 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 — helping build the controlled human evidence VIP still needs.