PE 22-28 — Basic Review Questions

1. What is PE 22-28, and how does it relate to spadin?

Answer: PE 22-28 is a synthetic heptapeptide (7 amino acids) corresponding to positions 22–28 of the sortilin (NTSR3) propeptide — commonly called "mini-spadin." It is a shortened analog of spadin (PE 12-28), a 17-amino-acid peptide released during maturation of sortilin that was the first identified TREK-1-blocking antidepressant peptide. PE 22-28 was designed from blood degradation products of spadin to be a more potent and more stable active core, and its key analog — G/A-PE 22-28, with a glycine→alanine substitution at the N-terminus — shows the most prominent neurogenic and antidepressant effects. Much of the foundational mechanism and safety data in the literature actually comes from the parent peptide spadin rather than from PE 22-28 itself.

2. What is the central tension a practitioner must understand about PE 22-28?

Answer: The TREK-1 target is genuinely validated in humans, but the drug is not. Genetic variants in the kcnk2 (TREK-1) gene track with antidepressant response in the large STAR*D cohort, and the preclinical antidepressant, neurogenic, and anti-inflammatory data for PE 22-28 are striking — yet the drug itself has never been tested in a human. There are zero clinical trials (no Phase 1/2/3), no human pharmacokinetic, dose-response, or safety data, no oral bioavailability, and much of the reassuring safety data is borrowed from spadin in rodents. A validated target plus strong preclinical drug data is not the same as a validated therapy, and that distinction is the single most important thing to convey.

3. What is TREK-1, and why does blocking it have an antidepressant rationale?

Answer: TREK-1 (encoded by kcnk2) is a background or "leak" potassium channel in the K2P family that helps set the resting membrane potential. When TREK-1 leaks potassium out of a neuron, the membrane hyperpolarizes and the cell fires less; an overactive TREK-1 therefore dampens activity — in the dorsal raphe nucleus that means less serotonin (5-HT) firing, linked to a depressive state. Blocking TREK-1 closes the leak, depolarizes the membrane, and increases neuronal excitability and 5-HT firing. The depression link is well supported: TREK-1 knockout mice are depression-resistant, sortilin-deficient mice (with reduced TREK-1 activity) show less depressive behavior, fluoxetine inhibits human TREK-1 at therapeutic concentrations, and kcnk2 variants track with antidepressant response in humans. Dr. Seeds emphasizes TREK-1 as an emerging CNS channel likely to matter increasingly in brain, spinal cord, and nervous-system therapeutics.

4. How does PE 22-28 work, from its primary target through its downstream effects?

Answer: PE 22-28 is an ultra-potent (IC_{50} ~0.12 nM — 300–500× more potent than spadin) and highly selective TREK-1 antagonist, with no effect on TREK-2, TRAAK, TRESK, or TASK-1, and a long ~23-hour duration of action. By blocking the TREK-1 leak current it depolarizes neurons and raises dorsal-raphe 5-HT firing, enhancing serotonergic transmission — importantly, WITHOUT inhibiting the serotonin transporter (SERT), a different route than SSRIs. Downstream it activates MEK/ERK (synaptic

plasticity) and PI3K/Akt (anti-apoptotic, pro-survival), and drives the PKA–pCREB–BDNF axis (PKA phosphorylates CREB → BDNF transcription → TrkB activation), producing rapid BDNF upregulation within hours. It also upregulates synaptogenesis markers (PSD-95, synapsin) and, via TREK-1 on astrocytes, suppresses NF-κB-mediated activation of neurotoxic A1 reactive astrocytes (lowering C1q, TNF-α, IL-1α) for a neuroprotective, anti-inflammatory effect.

5. What is the significance of the 4-day neurogenesis finding?

Answer: In mice, sub-chronic PE 22-28 induced hippocampal neurogenesis (roughly doubling $BrdU^+$ cells in the dentate gyrus) within 4 days, compared with the ~21 days SSRIs require — driven by the pCREB → BDNF → TrkB → MAPK/ERK cascade, with the G/A analog most potent. This matters because the slow (~21-day) neurogenesis of SSRIs mirrors their delayed clinical onset; a rapid-acting agent could, if it translated to humans, shorten antidepressant onset. This is the basis for the most discussed clinical concept for PE 22-28 — using it as a short-term bridge to cover the dangerous early weeks of SSRI therapy before the SSRI takes effect. The crucial caveat: this is all BrdU labeling in mouse hippocampus, with no human neurogenesis data for any spadin analog.

6. What does the human evidence actually consist of?

Answer: The only human evidence — and the highest evidence tier in this dataset — is genetic, not interventional. In the STAR*D trial population (the largest antidepressant pharmacogenomics study), Perlis et al. (2008) found four SNPs in the kcnk2 (TREK-1) gene associated with antidepressant treatment response. This validates TREK-1 as a real human depression target and helps explain why a TREK-1 blocker is of interest, but it does NOT test or validate PE 22-28 in any human. SNP association is not therapeutic equivalence. Everything else — the antidepressant behavioral models (forced swim test, novelty-suppressed feeding, learned helplessness, corticosterone model), the neurogenesis, synaptogenesis, and NF-κB/astrocyte data — is from rodent or in-vitro studies, several of them using spadin rather than PE 22-28.

7. What is known about safety, and why is TREK-1's biology "double-edged"?

Answer: The available safety data is favorable but comes mostly from the parent peptide spadin (PE 12-28), not PE 22-28, and entirely from rodents: no cardiac dysfunction (no IKr/IKs blockade), no effect on blood pressure or pulse, no glycemia changes, no change in cardiac infarct size after three-week treatment, no off-target channel activity, and enhanced (not worsened) seizure resistance — with PE 22-28 possibly even more seizure-protective. None of this is human data, and it should not be extrapolated to PE 22-28 without direct study. TREK-1's biology is double-edged because the channel does far more than regulate mood: it contributes to ischemic neuroprotection (so blockade could theoretically impair ischemic tolerance in stroke or cardiac ischemia), is expressed in cardiac tissue (unknown effects of chronic blockade on rhythm/conduction) and smooth muscle (possible vascular/blood-pressure effects), and modulates pain and temperature (possible hyperalgesia or thermoregulatory changes). Chronic use may also cause receptor desensitization. All of these are theoretical, uncharacterized risks that follow directly from the mechanism.

8. How is PE 22-28 used in practice, and what should guide responsible use?

Answer: There is no FDA-approved or validated human use — no IND, no GMP standard, and as a peptide it has no oral bioavailability, so it requires parenteral or intranasal delivery. Dr. Seeds describes an anecdotal intranasal practice pattern (with the explicit caveat that no human standards exist): a formulation around 4 mg/mL, where one spray delivers roughly 400 mcg, dosed about 400–800 mcg per nostril once daily, for depression and anxiety — used specifically as a short-term bridge alongside an SSRI to make the first weeks more tolerable, and given only for a short period since any benefit should appear quickly. These are anecdotal observations, not a validated protocol, with no human efficacy or safety data behind them. Responsible use means presenting the validated target and strong preclinical data honestly alongside the complete absence of human trials, PK, dosing, and safety data, the borrowed-from-spadin nature of the safety record, and TREK-1's double-edged biology; obtaining thorough informed consent; using only short courses with careful documentation (route, dose, response); and avoiding it in anyone with ischemic, cardiac, or relevant neurological risk. It is best understood as a probe of a promising target, not an established therapy.