CLINICAL LEARNING GUIDE

PE 22-28

"Mini-Spadin" | Selective TREK-1 Potassium-Channel Antagonist | Sortilin-Derived Heptapeptide

Mechanisms, Evidence, and Clinical Applications

Based on lecture materials by William Seeds, MD — SSRP Institute | Cellular Medicine Education

SECTION 1 · PROFILE OF THE PEPTIDE

Overview

PE 22-28 is a synthetic heptapeptide (7 amino acids) corresponding to positions 22–28 of the sortilin propeptide — often called "mini-spadin." It is a shortened analog of spadin (PE 12-28), a 17-amino-acid peptide released during maturation of sortilin/NTSR3 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, more stable active core, and a key analog — G/A-PE 22-28, with a glycine→alanine substitution at the N-terminus — shows the most prominent neurogenic and antidepressant effects.

Its defining feature is an unusual mechanism for an antidepressant: it is a selective antagonist of the TREK-1 potassium channel rather than a serotonin-reuptake inhibitor. It is extraordinarily potent and selective — an IC_{50} of about 0.12 nM at TREK-1 (300–500-fold more potent than spadin, and lower than fluoxetine's ~150 nM), with no inhibition of the related channels TREK-2, TRAAK, TRESK, or TASK-1 — and it acts for roughly 23 hours (vs ~7 for spadin) with greater plasma stability. The most eye-catching preclinical signal is rapid neurogenesis: it induces hippocampal neurogenesis within 4 days, compared with the ~21 days required for SSRIs.

PE 22-28 occupies a specific and instructive position the practitioner must hold in full. The TREK-1 target itself is genuinely validated in humans — 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 are striking. But the drug has never been tested in a human: there are zero clinical trials, no human pharmacokinetics, dose-response, or safety data, no oral bioavailability, and much of the quoted safety data actually comes from the parent peptide spadin rather than PE 22-28. Dr. Seeds is enthusiastic about TREK-1 as an emerging CNS channel and describes an anecdotal intranasal practice use (as a short-term bridge alongside SSRIs), but he is clear that no human standards exist. A validated target and strong preclinical data are not the same as a validated drug, and that distinction is the central thing to convey.

Peptide Profile

Property	Detail
Name	PE 22-28 ("mini-spadin"); key analog G/A-PE 22-28 (N-terminal Gly→Ala)

Property	Detail
Identity / origin	Synthetic heptapeptide; positions 22–28 of the sortilin (NTSR3) propeptide; shortened analog of spadin (PE 12-28)
Target	Selective TREK-1 (kcnk2) potassium-channel antagonist; no effect on TREK-2, TRAAK, TRESK, TASK-1
Potency	IC_{50} ~0.12 nM (spadin 40–60 nM; fluoxetine ~150 nM); ~55% TREK-1 inhibition at 100 nM
Duration / stability	~23 h action (spadin ~7 h); greater resistance to plasma degradation than spadin
Signature effect	Hippocampal neurogenesis within 4 days (vs ~21 days for SSRIs)
Routes (preclinical)	IP, IV, ICV, oral gavage in rodents; parenteral/intranasal required (peptide — no oral bioavailability)
Human PK/dose	NONE — no human pharmacokinetics, dose-response, or safety data
Human evidence	ZERO clinical trials; one human genetic cohort (STAR*D kcnk2 SNPs) supports the target, not the drug
Regulatory	NOT FDA-approved; no IND; research compound only

Where PE 22-28 Sits

Within the neuroprotection group, PE 22-28 is the channel-targeted, mood-and-neurogenesis peptide — mechanistically distinct from the brain-derived hydrolysates (Cerebrolysin, Cortexin), the synaptogenic Dihexa, and the growth-factor analog IGF-1 LR3. Its closest relative in this work is its own parent, spadin, and conceptually it sits in the antidepressant space, but with a non-serotonergic-reuptake mechanism (TREK-1 blockade) that converges on the same downstream endpoints valued across this group: BDNF, CREB, synaptogenesis, neurogenesis, and reduced neuroinflammation. Dr. Seeds frames it less as a finished therapeutic and more as the leading probe of an emerging and important target — the TREK-1 background potassium channel — with a plausible near-term niche as a rapid-onset adjunct or bridge for depression and anxiety, pending the human data that does not yet exist.

> **⚠ PE 22-28 is NOT FDA-approved, has no IND, and is a research compound only. There have been ZERO human clinical trials and there is no human pharmacokinetic, dose-response, or safety data — essentially all evidence is from rodent models, with one human genetic cohort (STAR*D) that validates the TREK-1 target but NOT this drug. Much of the cited safety data is from the parent peptide spadin, not PE 22-28, and should not be assumed to transfer. There is no oral bioavailability, and any intranasal use is anecdotal with no established standards. TREK-1 also has protective roles (ischemia, cardiac, pain, thermoregulation), so blockade carries theoretical risks. Full informed consent is essential.**

SECTION 2 · MODES OF ACTION AND MECHANISMS

PE 22-28's mechanism begins at a single, well-defined molecular target — the TREK-1 potassium channel — and fans out into the serotonergic, neurotrophic, and anti-inflammatory cascades that underlie its antidepressant and neurogenic effects. Understanding the channel itself is the key to the whole peptide, which is why Dr. Seeds spends so much time on it.

The Target: the TREK-1 Background Potassium Channel

TREK-1 (TWIK-Related K^+ channel 1, encoded by kcnk2) is a background or "leak" potassium channel in the K2P family that helps set the resting membrane potential. The logic is straightforward once stated: when TREK-1 leaks potassium out of the neuron, the membrane hyperpolarizes and the cell fires less; an overactive TREK-1 therefore dampens neuronal activity — in the dorsal raphe nucleus, that means less serotonin (5-HT) firing, which is linked to a depressive state. Blocking TREK-1 closes the leak, depolarizes the membrane, and increases neuronal excitability and 5-HT firing. The depression connection 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 genetic variants in kcnk2 track with antidepressant response in humans (STAR*D). TREK-1 is expressed in the hippocampus, cortex, dorsal raphe, spinal cord, peripheral sensory neurons, cardiac tissue, and smooth muscle, and also participates in mechanosensitivity, thermosensitivity, ischemic neuroprotection, anesthesia, and pain — a breadth that matters for safety (see the note below).

Primary Mechanism: Selective TREK-1 Blockade

PE 22-28 selectively blocks the TREK-1 leak current, increasing membrane depolarization and neuronal excitability. It does so with ultra-high potency (IC_{50} ~0.12 nM; ~55% inhibition at 100 nM) and high selectivity (no effect on TREK-2, TRAAK, TRESK, or TASK-1 at therapeutic concentrations), and its effect lasts roughly 23 hours — a substantial improvement in both potency and stability over spadin.

Serotonergic Enhancement (Non-SERT)

Downstream of TREK-1 blockade, increased excitability in the dorsal raphe nucleus raises 5-HT neuron firing and enhances serotonergic transmission to the forebrain. Crucially, this complements but does NOT require serotonin-transporter (SERT) inhibition — PE 22-28 raises serotonergic tone by a different route than SSRIs, which is the basis for its claimed (theoretical) distinct side-effect profile.

Neurotrophic Cascades: MAPK/ERK, PI3K/Akt, and the PKA–pCREB–BDNF Axis

PE 22-28 engages the neurotrophic machinery common to this peptide group. It produces time- and concentration-dependent ERK activation (MEK/ERK → synaptic plasticity) and PI3K/Akt signaling (anti-apoptotic, pro-survival, synergistic with BDNF/TrkB). Most importantly, it drives the PKA–pCREB–BDNF axis: PKA phosphorylates CREB in the hippocampus, and pCREB drives BDNF gene transcription, producing rapid BDNF mRNA and protein upregulation within hours — an effect that is most prominent with the G/A-PE 22-28 analog. BDNF then activates TrkB, feeding back into the MAPK/ERK and PI3K/Akt pathways. Spadin work also shows upregulation of the synaptogenesis markers PSD-95 and synapsin and an increase in mature dendritic spines.

NF-κB / A1 Astrocytes / Neuroinflammation

A more recent thread links TREK-1 blockade to neuroinflammation. TREK-1 is expressed in astrocytes as well as neurons, and in a chronic-stress (CUMS) rat model, blocking TREK-1 inhibited NF-κB-mediated activation of A1 reactive astrocytes — the neurotoxic, synapse-destroying astrocyte state — by suppressing NF-κB nuclear translocation (Zhou 2023). The result was reduced neuroinflammatory markers (C1q, TNF-α, IL-1α), a shift away from A1-like toward neuroprotective A2-like astrocytes, and a net anti-inflammatory, neuroprotective

microenvironment — giving PE 22-28 a neuroprotective dimension beyond its antidepressant action.

Rapid Neurogenesis

The headline downstream effect is speed. PE 22-28 induces hippocampal neurogenesis (roughly doubling $BrdU^+$ cells in the dentate gyrus) within 4 days of sub-chronic treatment, versus the ~21 days SSRIs require — driven by the pCREB → BDNF → TrkB → MAPK/ERK cascade, with G/A-PE 22-28 most potent. Because the ~21-day neurogenic latency of SSRIs mirrors their clinical onset delay, a 4-day neurogenic effect — if it translated to humans — could shorten antidepressant onset, which is the basis for the "bridge" concept discussed later. All of this is BrdU labeling in mouse hippocampus, with no human neurogenesis data for any spadin analog.

> **Key mechanistic point: PE 22-28 is an ultra-potent (IC_{50} ~0.12 nM), highly selective TREK-1 potassium-channel antagonist. By blocking the TREK-1 leak current it depolarizes neurons and raises dorsal-raphe 5-HT firing — enhancing serotonergic tone WITHOUT inhibiting SERT — and engages MAPK/ERK, PI3K/Akt, and the PKA–pCREB–BDNF axis to drive rapid (4-day) hippocampal neurogenesis, synaptogenesis (PSD-95, synapsin), and NF-κB-mediated anti-inflammatory/anti-A1-astrocyte effects. The mechanism is coherent and the TREK-1 target is human-validated (STAR*D) — but the drug's mechanism data are entirely preclinical, and the same channel has protective roles that make blockade double-edged.**

A Note on TREK-1's Double-Edged Biology

The very feature that makes PE 22-28 attractive — potent, durable TREK-1 blockade — is also the source of its main theoretical risks, because TREK-1 is not only a mood channel. It mediates neuroprotection during ischemia (opening to dampen firing and protect tissue), so blocking it could in principle impair ischemic tolerance in stroke or cardiac ischemia. It is expressed in cardiac tissue (where chronic blockade's effects on rhythm and conduction are unknown), in smooth muscle (possible vascular/blood-pressure effects), and in sensory pathways (where it modulates pain and temperature, raising the possibility of hyperalgesia or thermoregulatory changes). None of these have been characterized for PE 22-28 in humans. Dr. Seeds also notes that chronic exposure may bring receptor desensitization — something suggested in the spadin literature — which would need evaluation. In short, a single highly selective target is elegant, but a channel with this many physiological jobs makes potent blockade inherently double-edged.

SECTION 3 · POINTS OF CLINICAL RELEVANCE

- **The defining tension.** A human-validated target and striking preclinical drug data — but zero human trials of the drug.

The TREK-1 target is genuinely validated in humans (kcnk2 variants track with antidepressant response in STAR*D), and PE 22-28's preclinical antidepressant, neurogenic, and anti-inflammatory data are impressive. But the drug itself has never been in a human — no clinical trials, no pharmacokinetics, no dose-response, no safety data — and much of the quoted safety data is borrowed from spadin. A validated target is not a validated drug.

- **Target validated, drug not.** Keep these two claims separate.

The STAR*D genetic association supports TREK-1 as a real human depression target, alongside TREK-1 knockout (depression-resistant) and sortilin-deficient mice and fluoxetine's

TREK-1 inhibition. None of this validates PE 22-28 as a human therapeutic. SNP association does not equal therapeutic equivalence — a distinction Dr. Seeds is careful to draw.

- **A genuinely novel mechanism.** TREK-1 blockade, not serotonin-reuptake inhibition.

PE 22-28 raises serotonergic tone by blocking a potassium leak channel and increasing dorsal-raphe firing, without touching SERT. This is mechanistically distinct from SSRIs and, in theory, could carry a different side-effect profile — though that profile is unproven in humans.

- **The headline: rapid (4-day) neurogenesis — and the SSRI-bridge idea.** Speed is the most clinically interesting signal.

Hippocampal neurogenesis within 4 days, versus ~21 days for SSRIs, is the standout finding. Because SSRI clinical onset tracks their slow neurogenesis, a rapid-acting agent could, if it translated, bridge the dangerous early weeks of SSRI therapy. This is the specific clinical role Dr. Seeds sees for it — a short-term adjunct to make the first weeks of an SSRI more tolerable — while stressing there is no human data to support it.

- **A neuroprotective, anti-inflammatory dimension.** TREK-1 blockade calms reactive astrocytes.

Beyond mood, TREK-1 blockade suppressed NF-κB-driven A1 reactive-astrocyte activation and lowered C1q, TNF-α, and IL-1α in a chronic-stress model, shifting astrocytes toward a neuroprotective phenotype. This broadens the rationale toward neuroprotection and the speculative neurodegeneration applications (AD/PD).

- **TREK-1's biology is double-edged.** The same blockade could be harmful in the wrong setting.

TREK-1 contributes to ischemic neuroprotection, cardiac and smooth-muscle function, and pain/thermal sensing. Blocking it could theoretically impair ischemic tolerance or affect cardiac rhythm, blood pressure, pain thresholds, or thermoregulation. These are theoretical, uncharacterized risks — but they follow directly from the mechanism.

- **The safety data isn't really PE 22-28's, and there's no human anything.** Most reassurance is borrowed from spadin.

The favorable safety findings (no cardiac toxicity, no glycemia changes, seizure resistance) come largely from spadin studies, not PE 22-28, and from rodents only. There is no human pharmacokinetic, dose-response, safety, or efficacy data, and no oral bioavailability. Any human use is fully investigational.

SECTION 4 · DOSING, DELIVERY, AND CURRENT-USE POSTURE

> **There is NO established human dosing for PE 22-28 and NO human pharmacokinetic data — every preclinical figure below is from rodent studies and is NOT translatable to humans. PE 22-28 is NOT FDA-approved and has no IND. As a peptide it has no oral bioavailability and requires parenteral or intranasal delivery. Any intranasal practice use is ANECDOTAL, with no established standards; it must be approached with full informed consent.**

Preclinical Dosing (Rodent — Not Translatable)

Route	Dose	Model / Setting	Outcome
IP (intraperitoneal)	3.0 µg/kg	Mouse, acute + sub-chronic	Antidepressant in FST and NSF
IV (intravenous)	10^{-6} M	Mouse, acute single dose	Reduced FST immobility
ICV (intracerebroventricular)	10^{-7} M	Mouse, acute	Highest efficacy — direct CNS
Gavage (oral)	1 mg/kg	Mouse, sub-chronic (4 day)	Active in FST (modified formulation)
In vitro (patch clamp)	100 nM	Cultured neurons	~55% TREK-1 inhibition
In vitro (synaptogenesis)	0.1 µM	Cultured cortical, 7–21 d	PSD-95 and synapsin upregulation

Pharmacokinetics & Delivery

- Action duration ~23 hours (vs ~7 h for spadin), with greater resistance to plasma degradation — a stability advantage of the shortened analog.
- No oral bioavailability: as a peptide it is subject to GI proteolysis, so parenteral or intranasal delivery is required; the G/A-PE 22-28 analog is reported to be favorable for stability.
- Intranasal delivery is the most discussed route for human use — a direct nose-to-brain pathway that could achieve CNS levels with limited systemic exposure — but human pharmacokinetics, bioavailability, and BBB penetration are all uncharacterized.

Evolving / Anecdotal Intranasal Practice (No Standards)

Unlike a purely laboratory compound, PE 22-28 is reportedly being used anecdotally in practice — always intranasally — and Dr. Seeds shares the pattern he has seen while stressing that no human standards exist and all of it is unvalidated. Typical reported use:

- Formulation around 4 mg/mL, where one spray delivers roughly 400 mcg; reported dosing has been about 400–800 mcg per nostril once daily.
- Targeted at depression and anxiety, and used specifically as a short-term bridge alongside an SSRI — the rationale being that the rapid (preclinical) neurogenesis and BDNF effect might make the first weeks of SSRI therapy (before the SSRI "kicks in") more tolerable.
- Used for a short period, since any benefit should appear quickly given the rapid neurogenic/BDNF signal; if used, Dr. Seeds urges documenting the intranasal route, dose, and response.

These are anecdotal observations, not a validated protocol; there is no human efficacy or safety data behind them, and the SSRI-combination idea in particular has no human validation. Other combinations (with anesthetics, analgesics, anti-epileptics) are entirely theoretical and uncharacterized for drug interactions.

SECTION 5 · EVIDENCE PROFILE

Preclinical Antidepressant & Mechanistic Evidence (Rodent / In Vitro)

Finding / Model	Compound / Setting	Result
Forced Swim Test (FST)	PE 22-28, 3.0 µg/kg IP	Significant ↓ immobility (91.8±6.1 s; p=0.0001)
FST — G/A analog	G/A-PE 22-28, 3.0 µg/kg IP	Most prominent effect; superior to parent PE 22-28
Novelty Suppressed Feeding	4-day sub-chronic	↓ latency to eat; comparable to chronic fluoxetine
Learned helplessness	Spadin analog	Reduced helpless behavior vs vehicle
Corticosterone model	PE 22-28, 3.0 µg/kg IP	Depression reversed (acute and sub-chronic)
Neurogenesis	Sub-chronic 4 days	$BrdU^+$ cells ~doubled in dentate gyrus (4 d vs 21 d for SSRIs)
Synaptogenesis	Spadin (in vitro + in vivo)	PSD-95 and synapsin up; more mature dendritic spines
NF-κB / astrocytes	CUMS rat model (Zhou 2023)	↓ A1 astrocytes, C1q, TNF-α, IL-1α; neuroprotective shift

The One Human Data Point: STAR*D Genetic Cohort

The single piece of 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. It does NOT test or validate PE 22-28 in any human, and SNP association is not therapeutic equivalence.

Mechanistic Checklist (Evidence-Tiered)

Axis	Status	Evidence Tier
TREK-1 blockade (selective, potent)	Confirmed	In vitro / animal
Serotonergic enhancement (DRN; non-SERT)	Confirmed	Animal
BDNF / pCREB / TrkB activation	Confirmed	Animal
Rapid (4-day) neurogenesis	Confirmed	Animal (mouse hippocampus)
Synaptogenesis (PSD-95, synapsin)	Confirmed	In vitro / animal (largely spadin)
NF-κB / A1-astrocyte anti-inflammation	Confirmed	Animal (CUMS rat)
TREK-1 as human depression target	Supported	Human genetic cohort (STAR*D)
Human antidepressant efficacy / safety	Unconfirmed	No human trials of the drug
Human PK, dose, oral bioavailability	Unconfirmed	No human data; no oral bioavailability

What Can and Cannot Be Confirmed

Can confirm	Cannot confirm
Selective, ultra-potent TREK-1 blockade (IC_{50} ~0.12 nM); ~23 h action	Any human efficacy, dose, or safety (no trials)
Antidepressant and rapid-neurogenic effects in rodents	Whether 4-day neurogenesis translates to humans
BDNF/pCREB and NF-κB/astrocyte effects (preclinical)	Human pharmacokinetics, BBB penetration, oral bioavailability
TREK-1 is a human-validated depression target (STAR*D)	That PE 22-28 is a validated human therapeutic
Favorable rodent safety — mostly from spadin	PE 22-28-specific or human safety; long-term effects (any species)

Critical Evidence Gaps

- Zero human clinical trials (no Phase 1/2/3); no human pharmacokinetics, dose-response, or safety data; no IND/GMP pathway established.
- No oral bioavailability; human BBB penetration uncharacterized; intranasal/parenteral delivery unvalidated in humans.
- Much safety data is from spadin, not PE 22-28, and should not be assumed to transfer; no long-term safety in any species.
- TREK-1's protective roles (ischemia, cardiac, pain, thermoregulation) create theoretical risks of blockade that are unstudied; possible receptor desensitization with chronic use.
- No head-to-head comparison with any SSRI/SNRI; the SSRI-bridge concept is anecdotal and unvalidated.

SECTION 6 · CLINICAL CONSIDERATIONS

Regulatory Status

PE 22-28 is not FDA-approved, has no IND on record, and is an investigational/research peptide only — there is no approved route to clinical use, no GMP manufacturing standard, and no FDA review. It is not available as an FDA-approved compounded product. Any human use is off-label/investigational and unsupported by an approved framework.

Safety Profile

The available safety data is favorable but must be read with a critical caveat: most of it comes from the parent peptide spadin (PE 12-28), not PE 22-28 itself, and all of it is from rodents. In spadin studies there was no cardiac dysfunction (no IKr/IKs blockade), no effect on blood pressure or pulse, no glycemia changes, no modification of cardiac infarct size after three-week treatment, and no off-target channel activity; both spadin and PE 22-28 enhanced (rather than worsened) seizure resistance, and PE 22-28 may be even more seizure-protective. None of this is PE 22-28-specific or human data, and it should not be extrapolated to PE 22-28 without direct study. There is no human safety data for any spadin analog.

Contraindications & Cautions (Theoretical)

- Ischemic conditions (stroke, cardiac ischemia): TREK-1 blockade may impair ischemic neuroprotection — theoretically harmful.

- Cardiac disease: TREK-1 is expressed in cardiac tissue; effects of chronic blockade on rhythm and conduction are unknown.
- Pain and thermoregulation: TREK-1 modulates nociception and thermosensation — possible hyperalgesia, pain dysregulation, or temperature effects.
- Drug interactions: unknown and theoretical, especially with SSRIs, anesthetics, analgesics, and anti-epileptics.
- Chronic use: possible TREK-1 receptor desensitization over time (suggested in spadin work); long-term CNS effects unstudied.

Monitoring (Theoretical)

No human monitoring protocols exist; the following are prudential extrapolations from TREK-1's biology that would apply to any future human study: baseline and periodic ECG (cardiac TREK-1); seizure history and EEG (despite likely protective effects); pain-threshold and sensitivity assessment (nociception); fasting glucose/insulin (glucose homeostasis); body-temperature monitoring (thermosensitivity); cognitive, mood, and neurological assessment at each dosing interval; and delivery-site tolerability (intranasal/injection). These are research-design considerations, not validated clinical monitoring.

Patient Selection & Practitioner Posture

There is no validated human use, so patient selection is necessarily cautious and investigational. The clearest conceptual niche — and the one Dr. Seeds describes anecdotally — is as a short-term, intranasal adjunct or bridge for depression/anxiety alongside an SSRI, exploiting the rapid (preclinical) neurogenic effect to cover the early weeks before an SSRI takes effect. The responsible posture is to present 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; to obtain thorough informed consent; to use only short courses with careful documentation; and to avoid 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.

SECTION 7 · A FINAL NOTE

PE 22-28 is one of the more conceptually elegant peptides in the neuroprotection group: a sortilin-derived heptapeptide — "mini-spadin" — that hits a single, well-defined molecular target, the TREK-1 background potassium channel, with extraordinary potency (IC_{50} ~0.12 nM) and selectivity. By closing the TREK-1 leak it depolarizes neurons and raises dorsal-raphe serotonin firing without touching the serotonin transporter, and it drives the PKA–pCREB–BDNF axis, MAPK/ERK and PI3K/Akt signaling, synaptogenesis, and an NF-κB-mediated anti-inflammatory shift away from neurotoxic A1 astrocytes. Its signature is speed: hippocampal neurogenesis within 4 days, against the ~21 days SSRIs require — the basis for its most interesting potential use as a rapid-onset bridge. And uniquely in this group, its target is genuinely validated in humans through the STAR*D genetic data.

And yet the honest accounting is unambiguous. The target is validated; the drug is not. There are zero human clinical trials, no human pharmacokinetics, dose-response, or safety data, and no oral bioavailability — and much of the reassuring safety record actually belongs to the parent peptide spadin, not PE 22-28, and to rodents only. TREK-1's many physiological roles — in ischemic neuroprotection, the heart, smooth muscle, pain, and thermoregulation — make potent blockade double-edged, and chronic use may bring receptor desensitization. The estimated timeline even to a first-in-human Phase 1 study is measured in years.

For the practitioner, the posture follows from that gap. PE 22-28 is a compelling probe of an emerging and important target, with a plausible near-term niche as a short-term intranasal bridge for depression/anxiety alongside an SSRI — a use Dr. Seeds has seen anecdotally (roughly 400–800 mcg per nostril once daily) but which rests on no human data and no standards. Used at all, it should be used investigationally, intranasally, short-term, with full informed consent that names the absence of human evidence and TREK-1's double-edged biology, while avoiding patients with ischemic, cardiac, or relevant neurological risk — and documenting everything, because the human evidence base for this peptide does not yet exist. Dr. Seeds's larger point is worth keeping: TREK-1 itself is an emerging channel likely to matter increasingly in brain, spinal cord, and nervous-system therapeutics.

> **Bottom line: PE 22-28 ("mini-spadin") is an ultra-potent (IC_{50} ~0.12 nM), highly selective TREK-1 potassium-channel antagonist that raises serotonin firing WITHOUT inhibiting SERT and drives the PKA–pCREB–BDNF axis, with rapid (4-day) hippocampal neurogenesis, synaptogenesis, and NF-κB/A1-astrocyte anti-inflammation — ~23 h action and 300–500× spadin's potency. The TREK-1 target is human-validated (STAR*D kcnk2 SNPs), but the DRUG has had ZERO human trials — no human PK, dose, or safety data, no oral bioavailability, and most "safety" data is borrowed from spadin in rodents. TREK-1's protective roles (ischemia, cardiac, pain, thermal) make blockade double-edged. NOT FDA-approved; no IND. Anecdotal intranasal use as a short-term SSRI bridge (~400–800 mcg/nostril daily) exists but is unvalidated. A validated target with a promising preclinical drug — not yet a validated therapy.**

Selected References & Source Note

This guide was prepared from the recorded SSRP lecture on PE 22-28 by William Seeds, MD, and the accompanying slide deck. The 12 references below are reproduced from the lecture's bibliography; all are animal, in-vitro, or review sources except one human genetic cohort (Perlis 2008, STAR*D). Several foundational findings derive from the parent peptide spadin (PE 12-28). Readers should consult the primary sources directly.

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