# Humanin (HN)

A Clinical Learning Guide for Medical Providers

*Mitochondrial-Derived Peptide (MDP) • 24 Amino Acids • Encoded in MT-RNR2*

**Evidence base at a glance: Robust and reproducible PRECLINICAL data (in vitro and animal) — but ZERO completed human randomized controlled trials for any indication. All clinical use is investigational and off-label.**

## 1. Peptide Profile

**Full name:** Humanin (HN)
**Classification:** Mitochondrial-derived peptide (MDP) — the founding and most extensively studied member of the class
**Encoding gene:** MT-RNR2 — a short open reading frame (ORF) within the mitochondrial 16S ribosomal RNA region
**Size:** 24 amino acids (mitochondrial translation form) / 21 amino acids (cytoplasmic translation form)
**Discovery:** 2001, by Hashimoto et al. — cloned from the surviving neurons of an Alzheimer's disease brain
**Detection:** Measurable in plasma, cerebrospinal fluid (CSF), and tissues; secreted via a pseudo-signal peptide so it acts both intracellularly and extracellularly
**Conservation:** Highly conserved from C. elegans through mice, primates, and humans — pointing to an ancient, fundamental biological role
**Age relationship:** Circulating levels decline progressively with age; children of centenarians show elevated levels versus age-matched controls

### Key Analogues

| Analogue | Modification | Significance |
|---|---|---|
| **HNG (S14G-HN)** | Ser14 → Gly substitution | ~1000× more potent than native HN; the form used in most preclinical research, so much published data is HNG-derived, not native HN |
| **HNGF6A** | S14G + Phe6 → Ala | Does not bind IGFBP-3; superior insulin-sensitizing / metabolic effect |
| **F6A-HN** | Phe6 → Ala | Removes IGFBP-3 binding; enhanced central metabolic effects |

**Structurally important residues**

- **Cys8:** essential for biological activity
- **Ser14:** the S14G substitution creates the high-potency HNG analogue
- **Phe6:** the F6A substitution removes IGFBP-3 binding and enhances metabolic effect

## 2. Modes of Action & Mechanisms

Humanin is a mitochondrial "stress-response" signal: rather than being constitutively active, MDPs are made available to protect the cell when the mitochondria are under stress. Its protective actions converge on apoptosis suppression, cytoprotection, and metabolic signaling through two receptor systems and several intracellular partners.

### Receptor Systems

**Receptor 1 — CNTFR / WSX-1 / gp130 (IL-6 receptor family trimeric complex)**

- HN induces hetero-oligomerization of the three subunits

- Knockdown of CNTFR or WSX-1 abolishes HN-mediated cytoprotection — confirming this receptor is required
- Downstream: JAK2/STAT3, ERK1/2, PI3K/AKT — dominant in neurons

**Receptor 2 — FPRL1 (seven-transmembrane GPCR)**

- HN competitively antagonizes amyloid-β (Aβ42) at this receptor
- Downstream: calcium mobilization and ERK1/2 — more relevant in immune/inflammatory contexts

### Intracellular Binding Partners

- **Bax:** HN sequesters Bax in the cytoplasm, blocking its translocation into the mitochondria and thereby inhibiting intrinsic apoptosis
- **IGFBP-3:** HN antagonizes IGFBP-3-induced apoptosis (pro-survival); IGFBP-3 in turn tempers HN's metabolic effects — a key bidirectional regulatory node

### Downstream Signaling Cascades

| Pathway | Primary Function | Notes |
|---|---|---|
| **JAK2 / STAT3** | Neuroprotection (essential) | STAT3 phosphorylation required; HNG activates STAT3 in OLD but not young hippocampus |
| **PI3K / AKT** | Cell survival, anti-apoptosis | Promotes Bcl-2 regulation, caspase-3 inhibition, BFL-1 upregulation; stronger in aged mice |
| **ERK1/2** | Synaptic plasticity & memory | Enhances memory-related signaling; cognitive improvement in aged rodents |
| **AMPK / eNOS** | Cardioprotection | Mediates ~50% reduction in myocardial infarct size; route-independent |

**Chaperone-like anti-amyloid activity**

HN inhibits toxic Aβ oligomerization (without preventing mature fibril formation), behaving as a chaperone that routes misfolded protein toward autophagy and degradation. The same chaperone activity acts against IAPP (islet amyloid polypeptide) misfolding implicated in pancreatic β-cell toxicity in type 2 diabetes.

## 3. Points of Clinical Relevance

### 1. Multi-organ, pleiotropic protection from a single mitochondrial signal

Humanin acts protectively across brain, heart, retina, and metabolic tissue through overlapping pathways (JAK/STAT3, PI3K/AKT, ERK1/2, AMPK/eNOS). This breadth is the central reason for clinical interest — but it also means effects are diffuse and difficult to isolate to a single validated indication.

### 2. The anti-apoptotic mechanism is also the principal safety concern

Bax sequestration, caspase-3 inhibition, and Bcl-2 modulation are the same survival mechanisms exploited by cancer cells. This makes active or prior malignancy a theoretical contraindication and is the single most important risk to disclose. The oncological risk has NOT been characterized in humans.

### 3. Most published efficacy data come from HNG, not native Humanin

The highly potent HNG analogue (≈1000×) underlies the majority of dramatic preclinical results. Extrapolating those findings to native HN — the peptide most likely to be discussed for clinical use — is unvalidated, and clinicians should not assume equivalence.

### 4. Centenarian association is striking but is association, not proven causation

Children of centenarians show elevated HN, and a specific SNP (rs2854128) linked to lower circulating HN tracks with accelerated cognitive aging and cardiovascular disease. Whether HN drives longevity or simply marks healthy aging remains unresolved — an important nuance when counseling longevity-focused patients.

5. **Retinal protection (AMD) is the application closest to clinical translation**
   HN protects retinal pigment epithelial (RPE) cells from oxidative stress, senescence, and mitochondrial dysfunction in vitro, with a clear mechanistic basis (STAT3, caspase-3 inhibition, TFAM upregulation, increased mtDNA copy number). Given AMD's role as a leading cause of blindness in aging, this is a rational near-term target.

6. **Short half-life is the dominant practical barrier**
   Native HN has a plasma half-life of roughly 5–15 minutes, which limits systemic utility and would require high-frequency dosing or sustained-release formulations. An open mechanistic question is whether brief signaling is actually sufficient to trigger the protective pathways — meaning the half-life may matter less than assumed.

7. **There are no human dosing guidelines — all use is investigational**
   No clinical protocols exist for dose, frequency, route, or duration. Circulating HN is measurable by ELISA but has no validated reference ranges, so it cannot yet guide therapy. Any clinical use requires full informed consent framed explicitly as experimental.

## 4. General Dosing & Delivery Options

**No validated human dosing exists. Everything below is preclinical or reflects evolving, anecdotal clinical practice — presented for educational context only, not as a treatment protocol.**

### Pharmacokinetics

**Native HN half-life:** ~5–15 minutes (rapid degradation)
**HNG half-life:** Improved stability vs native HN; exact t½ not well characterized
**Dose-response:** Bell-shaped for some endpoints — exceeding the optimal window may reduce or reverse efficacy
**Therapeutic window:** Relatively wide in rodents (efficacy across a 10–100× dose range)

### Routes Tested (Preclinical)

| Route | Notes |
|---|---|
| **IV (intravenous)** | 100% bioavailability; used in cardioprotection studies |
| **IP (intraperitoneal)** | Most common preclinical route; efficacy equivalent to IV |
| **ICV (intracerebroventricular)** | Required for central metabolic studies; bypasses the blood–brain barrier |
| **Intrathecal** | Used to bypass the BBB for CNS effects |
| **Intranasal** | Effective for CNS delivery; non-invasive alternative |

### Evolving Clinical Dosing Framework (anecdotal)

Where native HN is used clinically at all, observed practice sits in the range of approximately 250–500 mcg, with cycling schemes (e.g. three days per week over several-month frames, sometimes paired with other mitochondrial peptides) borrowed from how related MDPs are handled. The educator is explicit that whether these doses are effective — and whether perceived benefit is real or anecdotal — is genuinely unknown.

### Future Formulation Directions

- PEGylation to extend half-life
- Nanoparticle encapsulation
- Sustained-release delivery systems

## 5. Evidence Profile

### Confirmed Mechanisms (preclinical)

| Mechanism | Status | Tier |
|---|---|---|
| **Neuroprotection** | Confirmed in vitro and in vivo | Animal / In Vitro |
| **Cardioprotection** | Confirmed in animal MI-reperfusion models (~50% infarct reduction) | Animal Study |
| **Metabolic / insulin sensitization** | Confirmed central (hypothalamic, STAT3-dependent) mechanism | Animal Study |
| **Anti-apoptotic activity** | Confirmed — Bax binding, caspase-3 inhibition | In Vitro |
| **Anti-inflammatory** | Confirmed — cytokine modulation (IL-6↓, IL-10 modulated) | Animal Study |
| **Mitochondrial function** | Confirmed — bioenergetics restoration | In Vitro |

### Representative In Vivo Neuroprotection Data

| Model | Treatment | Outcome |
|---|---|---|
| **3xTg-AD mice** | HNG 5–50 µg/kg IP, 4–12 wks | Reduced Aβ plaque; improved spatial learning & memory |
| **Cognitive aging (18-mo mice)** | HNG 4 mg/kg IP 2×/wk | Improved cognition; AKT & ERK activated in old hippocampus only |
| **Neuroinflammation** | HNG systemic | Reduced microglial activation; IL-6↓ |
| **Neuropathic pain (2025)** | HN 4 mg/kg IP × 15 d | Attenuated pain across STZ, oxaliplatin, sciatic-cuff models |

### Human Evidence

- **Observational / correlative only:** SNP rs2854128 (lower HN) tracks with accelerated cognitive aging and CVD; HN reduced in AD and MELAS patients; centenarian-offspring elevation
- **Phase I:** Single IV dose up to 10 mg in healthy volunteers — no serious adverse events; mild, transient effects only
- **Phase II / III:** None

**CRITICAL GAPS — there is ZERO human interventional evidence for cognitive, cardiovascular, metabolic, or longevity benefit. No RCTs in any human disease. Human dosing not established. Long-term safety unknown. PK/PD not optimized for humans. Oncological risk not characterized. Delivery (short half-life) unresolved.**

## 6. Clinical Considerations

### Theoretical Contraindications

(No human data exist to confirm or refute these — they follow from mechanism.)

- **Active malignancy:** the anti-apoptotic mechanism could theoretically promote tumor cell survival — avoid
- **Prior malignancy:** risk unknown; insufficient data for guidance
- **Pregnancy & lactation:** no reproductive safety data in humans — avoid until data available

### Monitoring Parameters

- Circulating HN is measurable by ELISA, but no validated reference ranges exist — it is not yet a usable treatment-response biomarker
- Standard metabolic panel and CBC recommended if used investigationally, per clinical judgment

- Consider baseline and on-treatment circulating HN levels, recognizing the data cannot yet be interpreted against a reference standard

### Comprehensive Safety Profile

| Parameter | Finding | Tier |
|---|---|---|
| **Acute toxicity (animal)** | No toxicity at >100× therapeutic dose; wide safety margin | Animal Study |
| **Chronic safety (6-month)** | No significant adverse effects across routes | Animal Study |
| **Immunogenicity** | No antibody formation; no immune sensitization | Animal Study |
| **Fertility / reproductive** | No fertility or reproductive toxicity observed | Animal Study |
| **Phase I (human)** | IV single-dose ≤10 mg; no SAEs; mild headache, rare nausea | Phase I (limited) |
| **ECG / laboratory** | No attributable ECG or lab abnormalities in Phase I | Phase I (limited) |
| **Anti-apoptotic / oncological** | Theoretical tumor-survival concern — NOT characterized in humans | Theoretical |
| **Long-term human safety** | Completely unknown beyond limited Phase I | Data Gap |

### Unresolved Questions Clinicians Should Know

- **Translation site:** whether HN is synthesized predominantly at mitochondrial or cytoplasmic ribosomes is still debated in humans
- **Receptor hierarchy:** CNTFR/WSX-1/gp130 (neurons) vs FPRL1 (immune/inflammatory) — tissue dominance not defined, so the same dose may produce tissue-dependent effects
- **Bell-shaped dose-response:** exceeding the optimal window may blunt or reverse benefit; the human window is undefined
- **Native HN vs HNG:** clinical extrapolation from the potent analogue to native peptide is unvalidated

### Regulatory Status

Humanin is NOT FDA-approved for any indication. It is a research peptide; any clinical use is experimental and off-label by definition, requiring full informed consent. The educator's explicit position: benefit of any Humanin regimen in clinical practice cannot currently be confirmed.

## 7. Final Note

Humanin occupies an unusual place in peptide medicine: the preclinical case is genuinely compelling — multi-organ protection, ~50% infarct reduction, plaque reduction and cognitive gains in aged rodents, RPE protection, and an intriguing centenarian association — yet the human translational case is, at present, essentially empty. There are no completed RCTs, no established dosing, and an unresolved theoretical oncological risk built into its core mechanism.

For the practicing clinician, the honest framing is twofold. First, Humanin is best understood as a window into the broader biology of mitochondrial-derived peptides — a class (alongside MOTS-c and the SHLPs) that reframes the mitochondrial genome as an active signaling source and may eventually allow complementary targeting of metabolic, neurological, and cardiovascular axes. Second, until Phase II/III data, validated dosing, and oncological safety characterization exist, any clinical use remains strictly investigational, and patients asking about Humanin for anti-aging or longevity should be told plainly that no clinical benefit has yet been demonstrated.

**Bottom line: Mechanistically rich and worth following closely — but clinically unproven. Compelling preclinical signal; zero confirmed human benefit; investigational use only with full informed consent.**

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