CLINICAL LEARNING GUIDE

GHRP-6

Growth Hormone-Releasing Peptide-6

Mechanisms, Evidence, and Clinical Applications

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

SECTION 1 · PROFILE OF THE PEPTIDE

Overview

GHRP-6 (Growth Hormone-Releasing Peptide-6) is a synthetic hexapeptide growth hormone secretagogue. It was the first-generation GHRP, developed from met-enkephalin analogs by Cyril Bowers in the 1980s, and it most closely mimics ghrelin — the body's own gut-derived GH-releasing peptide. Like the other GHRPs it stimulates pulsatile, physiologic GH secretion, but two features set it apart: it is the strongest appetite stimulator of the class, and it has the most pronounced dual-receptor character, acting meaningfully on both the GHS-R1a (ghrelin) receptor and the CD36 scavenger receptor.

That CD36 activity is the basis for GHRP-6's unusually broad GH-independent profile — cardioprotection, multi-organ cytoprotection, antifibrotic effects in liver and skin, wound healing, and prokinetic (GI motility) effects. As with all the secretagogues, it amplifies the body's own GH rather than replacing it, preserving the pituitary feedback loops that exogenous GH bypasses.

Peptide Profile

Property	Detail
Generic Name	GHRP-6 (Growth Hormone-Releasing Peptide-6)
Classification	Synthetic hexapeptide (6 amino acids) GH secretagogue; ghrelin-receptor agonist
Sequence	His-D-Trp-Ala-Trp-D-Phe-Lys-NH_2 (MW 872.44 Da)
Generation / Origin	First-generation GHRP; derived from met-enkephalin analogs (Bowers, 1980s)
Receptors	GHS-R1a (ghrelin receptor) — primary; CD36 scavenger receptor — notably strong for this peptide
Route of Administration	Subcutaneous (clinical); IV bolus (PK studies)
Half-Life	Short — minutes (~3–5 min IV; somewhat longer SC)
GH Peak	~15–30 minutes post-injection
FDA Status	NOT approved — research compound; status varies by jurisdiction
Anti-Doping	WADA-prohibited at all times — Class S2 (Peptide Hormones, GH secretagogues)

Where GHRP-6 Sits Among the GH Secretagogues

The GH secretagogues split into two receptor families. The GHRH analogs (sermorelin, Mod GRF 1-29, CJC-1295, tesamorelin) act on the GHRH receptor. The GHRPs — GHRP-6, GHRP-2, hexarelin, and ipamorelin — act on the ghrelin receptor (GHS-R1a), and the non-peptide MK-677 acts there too. GHRP-6 is the first-generation, most ghrelin-like member; GHRP-2 followed as a more potent GH releaser; hexarelin sits between them with strong cardiac CD36 effects; and ipamorelin is the clean, selective third-generation standard. Because the GHRPs and GHRH analogs work through separate receptors on the same somatotroph, combining the two is synergistic.

> ⚠ **GHRP-6 is not FDA-approved (a research compound) and is WADA-prohibited at all times. All clinical use is off-label and investigational, and competitive (drug-tested) athletes must avoid it entirely.**

SECTION 2 · MODES OF ACTION AND MECHANISMS

GHRP-6 works through two receptors that do two different jobs. Through GHS-R1a it drives pulsatile GH release; through CD36 it produces a wide range of GH-independent, tissue-protective effects. The defining concept is that it amplifies the body's own physiologic GH while adding a second, protective signaling arm that the GHRH analogs and the cleaner GHRPs largely lack.

Receptor Mechanism: GHS-R1a Plus CD36

- **GHS-R1a (ghrelin receptor):** a G-protein-coupled receptor in the hypothalamus and pituitary. GHRP-6 acts as a super-agonist here — stronger than ghrelin itself — stimulating somatotrophs to release GH, promoting hypothalamic GHRH release, and reducing somatostatin's inhibitory tone. Its GH effect is primarily hypothalamic: it is blocked by hypothalamic-pituitary disconnection, and its synergy with GHRH requires an intact axis.
- **CD36 receptor:** a broadly expressed scavenger receptor (cardiovascular system, macrophages, adipocytes). Through CD36, GHRP-6 activates PPAR-γ and pro-survival signaling — the engine behind its cytoprotective and antifibrotic effects. This arm is more pronounced for GHRP-6 than for GHRP-2 or ipamorelin (hexarelin is the other strong CD36 binder).

Signaling Cascades

Pathway	Role
GHS-R1a → Gq/11 → PLC → IP3/DAG → Ca^{2+} + PKC	GH vesicle exocytosis (release)
Enhanced Na^{+} and L-type Ca^{2+} currents	Increases action-potential firing in somatotrophs (electrical activity)
PI3K / AKT1 → HIF-1α induction	Cell survival under hypoxic stress (cytoprotection)
CD36 → PPAR-γ → ↓ TGF-β1 / CTGF	Antifibrotic — reduces extracellular-matrix deposition
↑ Bcl-2 / ↓ Bax	Shifts the apoptotic ratio toward cell survival ($p<0.001$)
Antioxidant enzyme support	Reduces ROS, preserves mitochondrial integrity

GH Axis: Why Pulsatile Beats Continuous

GHRP-6 produces pulsatile GH that mimics the body's natural amplitude and raises IGF-1 through the liver, while preserving pituitary feedback. Compared with exogenous (injected) GH, this means physiologic pulses rather than a continuous square wave, a lower risk of GH-receptor desensitization, and the bonus of concurrent cytoprotective signaling. Dr. Seeds adds that consistent use can "entrain" the somatotrophs toward more efficient GH release that may persist after cycling off — and that the anabolic GH/IGF-1 drive helps counterbalance catabolism and sarcopenia (the AMPK–mTOR balance the series emphasizes).

> **Key mechanistic point: GHRP-6 is a dual-receptor peptide. The GHS-R1a arm amplifies physiologic, pulsatile GH (while lifting the somatostatin brake); the CD36 arm — via PPAR-γ — delivers GH-independent cytoprotection and antifibrosis. This second arm is what most distinguishes GHRP-6 from the other secretagogues.**

SECTION 3 · POINTS OF CLINICAL RELEVANCE

1. **Most potent orexigenic effect.** It is the strongest appetite stimulator of the GH secretagogues.

As the most ghrelin-like GHRP, GHRP-6 drives appetite more than GHRP-2, hexarelin, or ipamorelin (which is essentially neutral). This is a genuine advantage in cachexia, sarcopenia, post-surgical recovery, and the anorexia of aging — where restoring food intake matters. If appetite stimulation is unwanted (for example, when using it for anti-inflammatory ends), ipamorelin is the alternative. Dr. Seeds reframes the "disadvantage" of weight gain as often a metabolic benefit in the older, under-nourished patient.

2. **Broad tissue protection.** Its broad cytoprotection — cardiac and multi-organ — is its signature, via CD36.

In preclinical models GHRP-6 preserved cardiac function (preventing doxorubicin-induced fiber loss and ventricular dilation, reducing infarct-related fibrosis, sustaining mitochondrial integrity, and shifting Bcl-2/Bax toward survival), and protected liver, intestine, lung, and kidney in ischemia/reperfusion and multi-organ-failure models. It also produced a positive inotropic effect (stronger contraction) without raising heart rate.

3. **Antifibrosis through PPAR-γ.** It has robust antifibrotic and wound-healing effects.

Through CD36 → PPAR-γ, GHRP-6 down-regulates TGF-β1 and CTGF, reducing collagen and extracellular-matrix deposition. Preclinical work showed reduced liver-cirrhosis fibrosis, prevention of hypertrophic scarring, improved cutaneous wound healing and aesthetics, and reduced lung injury. Dr. Seeds notes a rational pairing with peptides like thymosin beta-4 (TB-4) and BPC-157 for collagen organization and scar work.

4. **Accelerates gut transit.** It has prokinetic (GI motility) effects.

GHRP-6 speeds gastric emptying and intestinal transit through a cholinergic, neuron-dependent pathway (the effect is abolished by atropine or vagotomy in animal models) — a useful property given how often impaired motility accompanies the conditions it is considered for.

5. **Dual-pathway GH amplification.** It synergizes with GHRH analogs.

GHRP-6 (GHS-R1a → Ca^{2+}) and a GHRH analog such as sermorelin (GHRH-R → cAMP/PKA) hit two independent cascades that converge on GH release, producing a response greater than the sum of the parts — with somatostatin suppression further enhancing the GHRH effect. This allows lower individual doses and a more physiologic pulse. The synergy depends on an intact hypothalamic-pituitary axis.

6. **Hormonal "spillover."** It raises cortisol and prolactin more than the other GHRPs — mildly and transiently.

GHRP-6 produces a transient, self-limiting rise in cortisol and prolactin that is more pronounced than with GHRP-2 or ipamorelin. It is expected rather than alarming, but it warrants baseline assessment and monitoring for sustained change.

7. **Understand the glucose/insulin interaction.** The transient glucose rise is an expected, benign efficiency effect — not a warning sign.

Like all GH secretagogues, GHRP-6 transiently antagonizes insulin and increases fat oxidation (beta-oxidation), which can cause a small, temporary glucose rise (reduced GLUT4-mediated uptake in muscle plus modest hepatic gluconeogenesis). Dr. Seeds frames this as the early signature of a system being pushed toward greater mitochondrial efficiency over months — not a red flag — but uncontrolled diabetes must be addressed first, ideally with a GLP-1 agent to set the metabolic foundation before a secretagogue is added.

SECTION 4 · GENERAL DOSING INSTRUCTIONS AND DELIVERY OPTIONS

> **GHRP-6 is not FDA-approved; use is off-label/investigational. The protocols below derive from clinical research and Dr. Seeds's practice frameworks. The subcutaneous route is the practical standard.**

Research / Clinical Dosing

Parameter	Protocol	Notes
Typical dose	100–300 mcg per injection (SC)	Lecturer's default is ~100 mcg; 1 mcg/kg is the ideal in human studies
Frequency	1–3× daily	Pulsatile dosing; GHRP-6 is usually given 2–3×/day
Timing	Fasted (no carbs/fats)	Carbohydrate and fat blunt the GH response
PK route (studies)	IV bolus 100–400 mcg/kg	Phase I dose-escalation, 9 healthy males
Half-life	Short (minutes)	Supports pulsatile dosing
Combination	With a GHRH analog (e.g., sermorelin)	Synergistic GH release

Dosing Philosophy: Hold the Dose, Use Frequency

As with the other GHRPs, the central concern is desensitization (tachyphylaxis) of the GHS-R1a receptor, and Dr. Seeds's consistent guidance is to anchor at 100 mcg per injection rather than chase higher numbers. Because GHRP-6 is a less potent GH releaser than GHRP-2 and tends to desensitize the receptor somewhat less, it tolerates a little more dosing room — and it is typically given two to three times daily rather than as a single nighttime dose:

- first thing in the morning, fasted;
- at night, at least two hours after dinner;
- optionally a third dose (e.g., post-workout) for three solid physiologic pulses.

Allow at least a 3-hour window between doses — the GH response curve needs roughly three hours to recalibrate, and dosing inside that window wastes the dose.

Cycling, Combinations, Administration

- Cycling: 5 days on / 2 days off, or 4 weeks on / 1 week off, or 12 weeks on / 4–6 weeks off — all aimed at protecting receptor sensitivity. Dr. Seeds treats cycling as individualized rather than fixed.
- Synergy with GHRH analogs: pair with sermorelin, Mod GRF 1-29, CJC-1295, or tesamorelin for a synergistic pulse. Dr. Seeds prefers a GHRP + GHRH pairing over stacking two GHRPs together.
- Antifibrotic/repair stacks: rationally combined with TB-4 and BPC-157 for collagen organization, scar reduction, and wound healing.
- Reconstitution & storage: reconstitute with bacteriostatic water; refrigerate at 2–8°C; use within ~28 days; protect from light.
- Timing & food: take fasted — no carbohydrate or fat within ~30 minutes after the dose, and ideally 1.5–2 hours of an empty stomach before. Pure protein (e.g., whey) does not blunt the response; black coffee is fine. Morning and bedtime are the natural fasted windows; keep timing consistent.

SECTION 5 · EVIDENCE PROFILE

Human Pharmacokinetics & GH Response

A Phase I dose-escalation study (Cabrales 2013) gave IV GHRP-6 at 100, 200, and 400 mcg/kg to nine healthy males. It produced a dose-related GH increase across all three doses, a short (minutes-long) half-life, was well tolerated with no serious adverse events, and showed enhanced tissue viability. This is the principal human dataset; the GH peak occurs ~15–30 minutes post-injection.

Cardioprotection & Cytoprotection — Preclinical

- Doxorubicin cardiomyopathy (rats): prevented myocardial fiber loss and ventricular dilation; preserved LV systolic function; sustained mitochondrial integrity; Bcl-2 up / Bax down ($p<0.001$).
- Ischemia/reperfusion & multi-organ failure (rats): protected liver, intestine, lung, kidney, and heart; ~3-fold increase in cell migration (migration-specific, not proliferation); neutrophil infiltration reduced 50–85%; lipid peroxidation reduced; added benefit when combined with EGF.
- Positive inotropic response without a chronotropic (heart-rate) effect, via calcium-channel action.

Antifibrotic & Wound Healing — Preclinical

Model	Key Finding
Liver cirrhosis (rats)	Fibrosis reduced via CD36 → PPAR-γ (TGF-β1/CTGF down)
Hypertrophic scar (rabbits)	Scar onset reduced / prevented
Cutaneous wounds (rabbits)	Improved healing and aesthetic outcome

Model	Key Finding
Acute lung injury (mice)	Reduced alveolitis and fibrosis

Comparative Analysis: GH Secretagogues

Peptide	Receptor	GH Release	Key Differentiator
GHRP-6	GHS-R1a + CD36	Strong	Strongest appetite; broad cytoprotection
GHRP-2	GHS-R1a (mild CD36)	Strongest	Most potent GH; less appetite
Hexarelin	GHS-R1a + CD36	Strong	Strong cardiac cytoprotection; desensitization risk
Ipamorelin	GHS-R1a	Moderate	Selective; minimal cortisol/prolactin/appetite
MK-677	GHS-R1a	Strong	Oral, long-acting non-peptide
Ghrelin	GHS-R1a	Moderate	Endogenous ligand; GHRP-6 is a super-agonist

Dr. Seeds's ordering: GHRP-2 gives the strongest GH release, hexarelin sits between GHRP-2 and GHRP-6, GHRP-6 is strong, and ipamorelin is moderate. For CD36/cytoprotection, GHRP-6 and hexarelin are the strong binders; GHRP-2 is milder; ipamorelin is minimal.

On Preclinical Evidence

Much of GHRP-6's non-GH evidence (cardioprotection, antifibrosis, wound healing) is preclinical — rats, rabbits, mice. Dr. Seeds's framing: the molecular pathways tend to cross species, so well-characterized mechanisms are informative even before human RCTs — but they remain mechanistic rationale, not proof, and controlled human trials are still needed.

Critical Evidence Gaps

- Most cardioprotective and antifibrotic evidence is preclinical; controlled human RCTs are lacking.
- No long-term human safety data beyond the Phase I PK study; chronic effects on cancer risk, glucose, and hormonal axes need study.
- Validated biomarkers for CD36-mediated effects, optimal non-GH dosing, and tissue-specific pharmacodynamics are not yet established.

SECTION 6 · CLINICAL CONSIDERATIONS

Contraindications

- Active or suspected malignancy — avoid GH stimulation.
- Uncontrolled diabetes mellitus — stabilize metabolism first (GLP-1 agents are the preferred bridge) before adding a secretagogue.
- Active pituitary pathology / tumors.
- Pregnancy and lactation.
- Known hypersensitivity to GHRP-6.

- WADA-tested athletes — prohibited at all times.

Adverse Effect Profile

Effect	Severity / Frequency	Notes
Increased appetite	Common; strongest of the class	Ghrelin-mimetic; benefit in cachexia, consideration otherwise
Cortisol elevation	Mild–moderate, transient	More than GHRP-2 / ipamorelin; self-limiting
Prolactin elevation	Mild, transient	Self-limiting; monitor for sustained change
Water retention / edema	Occasional	May present as nighttime wrist pain / carpal tunnel
Glucose elevation	Transient; monitor	GH-mediated insulin resistance (see Section 3)
Injection-site reaction	Mild, occasional	Redness, irritation

As with the GHRH/GHRP combinations, watch for fluid-retention-related carpal tunnel (nighttime wrist pain); long-term human safety data is limited.

Drug Interactions & Cautions

- Glucocorticoids may blunt the GH response.
- Insulin enhances the GH response (and GH in turn transiently opposes insulin).
- Carbohydrate and fat intake near dosing blunt GH release — dose fasted.
- Synergy with GHRH analogs is intended and beneficial; Dr. Seeds advises against stacking two GHRPs.

Patient Selection

Potential candidates: age-related GH decline (somatopause); sarcopenia/muscle-wasting; post-surgical recovery and tissue repair; cachexia with appetite deficit; impaired wound healing; and (research) cardioprotective protocols. GHRP-6's appetite and antifibrotic/repair profile make it particularly suited to under-nourished, catabolic, or wound-healing patients.

Pre-treatment workup: baseline IGF-1, fasting glucose, HbA1c, AM cortisol, prolactin, comprehensive metabolic panel, and body composition (DEXA or InBody). Document informed consent for off-label/research use.

Monitoring Framework

Timepoint	Assessment
Baseline	IGF-1, fasting glucose, HbA1c, AM cortisol, prolactin, comprehensive metabolic panel, body composition (DEXA/InBody)
Week 4	IGF-1 (target response), cortisol/prolactin; fasting glucose weekly ×4 then monthly; appetite/weight
Weeks 8–12	Body composition; reassess risk–benefit; monitor for tachyphylaxis
As indicated	Cardiac echo if used for cardioprotective indication (preclinical); quarterly reassessment

A note on IGF-1: useful as a trend (check no sooner than ~4 weeks, targeting an age-appropriate upper quartile), but a single value varies widely with timing, exercise, and the day — follow the trend and the clinical picture, not one number.

SECTION 7 · A FINAL NOTE

GHRP-6 is the original, most ghrelin-like growth hormone-releasing peptide — a first-generation hexapeptide that stimulates strong, pulsatile GH while acting as a super-agonist at the ghrelin receptor. But its defining feature is its dual-receptor reach: through CD36 and PPAR-γ it delivers a breadth of GH-independent effects — cardioprotection, multi-organ cytoprotection, antifibrosis, wound healing, and prokinetic GI action — that the cleaner secretagogues largely lack.

Its strongest appetite effect is a true clinical lever: a benefit in cachexia, sarcopenia, and the anorexia of aging, and a consideration to manage when appetite stimulation is not the goal (where ipamorelin is the alternative). Much of the cytoprotective and antifibrotic evidence is preclinical, and Dr. Seeds's honest framing is that well-characterized molecular pathways tend to cross species and are informative — but they remain mechanistic rationale until human trials confirm them.

The practical disciplines mirror the rest of the class: anchor the dose around 100 mcg and protect the receptor from desensitization (with a 3-hour window between pulses and sensible cycling); dose fasted; pair synergistically with a GHRH analog rather than stacking GHRPs; and treat the transient glucose rise and mild cortisol/prolactin spillover as expected, manageable consequences — provided metabolism (and uncontrolled diabetes in particular) is addressed first, often with a GLP-1 agent.

> **Bottom line: GHRP-6 is the first-generation, most ghrelin-like GHRP — a dual-receptor (GHS-R1a + CD36) peptide that amplifies physiologic, pulsatile GH while adding broad, GH-independent cytoprotection, antifibrosis, wound healing, and the strongest appetite stimulation of the class. Typically dosed at ~100 mcg SC, 2–3× daily fasted (with a 3-hour window), cycled, and synergistic with GHRH analogs. Watch for receptor desensitization, transient glucose elevation, water retention, and a mild-but-greater-than-peers cortisol/prolactin rise. A research compound; WADA-prohibited; investigational/off-label.**

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