



MOTS-c activator of the PGC-1 α pathway

MOTS-c is a mitochondrial-derived peptide that functionally interfaces with the AMPK–PGC-1 α axis and thereby influences mitochondrial biogenesis, metabolic flexibility, and stress resistance. [\[1\]](#) [\[2\]](#) [\[3\]](#) [\[4\]](#) [\[5\]](#)

Relationship to PGC-1 α

- PGC-1 α is a master **coactivator** that drives mitochondrial biogenesis and oxidative metabolism in tissues such as skeletal muscle, heart, and liver. [\[4\]](#)
- AMPK is an upstream kinase that activates PGC-1 α ; energy stress (e.g., exercise, caloric restriction) activates AMPK, which then promotes PGC-1 α transcription and activity. [\[3\]](#) [\[1\]](#)
- MOTS-c and PGC-1 α are linked bidirectionally: AMPK/PGC-1 α signaling regulates MOTS-c expression, and exogenous MOTS-c can in turn enhance PGC-1 α levels and PGC-1 α -dependent adaptations. [\[6\]](#) [\[1\]](#) [\[3\]](#) [\[4\]](#)

Evidence that MOTS-c modulates the PGC-1 α pathway

- In C2C12 myotubes, inhibition of AMPK or knockdown of PGC-1 α reduces MOTS-c expression, whereas PGC-1 α overexpression or recombinant MOTS-c supplementation increases MOTS-c mRNA and protein, indicating a regulatory loop involving AMPK/PGC-1 α and MOTS-c. [\[1\]](#) [\[3\]](#)
- In high-fat-diet obese mice, treadmill training increases skeletal-muscle levels of MOTS-c, PGC-1 α , and GLUT4 together with AMPK phosphorylation, suggesting that exercise and MOTS-c synergize through the AMPK–PGC-1 α pathway to improve insulin sensitivity and glucose uptake. [\[2\]](#) [\[3\]](#) [\[1\]](#)
- In diabetic cardiomyopathy models, MOTS-c treatment increases myocardial PGC-1 α protein, improves mitochondrial morphology and function, and reduces apoptosis, supporting a role for MOTS-c in promoting PGC-1 α -driven mitochondrial biogenesis and cardioprotection. [\[4\]](#)
- A more recent study reports that MOTS-c administration enhances skeletal-muscle mitochondrial bioenergetics in a manner dependent on PGC-1 α , again implicating MOTS-c as a modulator of PGC-1 α -mediated mitochondrial adaptations. [\[6\]](#)

Mechanistic picture (simplified)

- Upstream: Energy stress or exercise → activates AMPK → increases PGC-1 α → upregulates MOTS-c expression in skeletal muscle. [\[2\]](#) [\[3\]](#) [\[1\]](#)
- Feedback: Exogenous MOTS-c activates AMPK and improves mitochondrial function, which is associated with increased PGC-1 α expression and activity in muscle and heart tissue. [\[5\]](#) [\[7\]](#) [\[1\]](#) [\[4\]](#)
- Downstream: Enhanced PGC-1 α signaling increases mitochondrial biogenesis, oxidative capacity, GLUT4 expression, and antioxidant defenses, contributing to improved glucose metabolism, insulin sensitivity, and tissue protection. [\[8\]](#) [\[1\]](#) [\[2\]](#) [\[4\]](#)

Interpretation of “MOTS-c as a PGC-1 α activator”

- Current data support MOTS-c as an **indirect** activator/modulator of the PGC-1 α pathway rather than a classic small-molecule PGC-1 α agonist that binds the coactivator directly. [\[3\]](#) [\[1\]](#) [\[4\]](#)
- The primary nodes appear to be AMPK activation and mitochondrial stress-response signaling, with PGC-1 α upregulation observed as a key downstream effect that mediates many of MOTS-c’s metabolic and mitochondrial benefits. [\[7\]](#) [\[5\]](#) [\[1\]](#) [\[2\]](#)

If you tell me your context (e.g., basic understanding vs. designing experiments vs. therapeutic interest), I can tailor this to mechanisms, dosing paradigms in animal studies, or translational implications.

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peptide that would benefit this pathway

Two mitochondrial-targeted peptides with evidence of benefiting the **PGC-1 α pathway** are SS-31 (elamipretide) and MOTS-c. [\[9\]](#) [\[10\]](#) [\[11\]](#) [\[12\]](#) [\[13\]](#)

SS-31 (elamipretide)

- SS-31 is a tetrapeptide that binds cardiolipin in the inner mitochondrial membrane, stabilizing ETC supercomplexes and improving ATP production while lowering ROS. [\[11\]](#) [\[12\]](#) [\[13\]](#) [\[9\]](#)
- Beyond “repair,” several rodent and neuro models show SS-31 increases SIRT1 levels, enhances PGC-1 α nuclear translocation, and upregulates total PGC-1 α , thereby promoting mitochondrial biogenesis and function via the SIRT1–PGC-1 α axis. [\[12\]](#) [\[14\]](#) [\[11\]](#)

MOTS-c

- MOTS-c is a mitochondria-encoded peptide that acts systemically as a mitokine and activates AMPK, which is an upstream regulator of PGC-1 α . [\[15\]](#) [\[16\]](#) [\[10\]](#)
- In cell and animal models, MOTS-c treatment increases AMPK phosphorylation and PGC-1 α expression, improves mitochondrial bioenergetics, and reduces ROS and inflammatory cytokines via an AMPK–SIRT1–PGC-1 α pathway. [\[10\]](#) [\[17\]](#) [\[18\]](#) [\[15\]](#)

- Exercise and PGC-1 α overexpression both upregulate endogenous MOTS-c, and there is evidence that MOTS-c and endurance training act synergistically on AMPK/PGC-1 α signaling and insulin sensitivity. [\[19\]](#) [\[17\]](#) [\[9\]](#) [\[10\]](#)

Practical framing

- For directly targeting the **PGC-1 α axis**, MOTS-c is the more explicit upstream activator (via AMPK/SIRT1), whereas SS-31 primarily optimizes mitochondrial structure and redox state but also secondarily boosts SIRT1/PGC-1 α signaling in some models. [\[13\]](#) [\[14\]](#) [\[10\]](#) [\[11\]](#) [\[12\]](#)
- All peptide use here is off-label for longevity; human data are still limited, so any protocol should ideally be in consultation with a clinician and layered on top of the cornerstone "activator" of PGC-1 α : endurance-type exercise. [\[20\]](#) [\[21\]](#) [\[9\]](#)

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MOTS-c What would an effective dose be for humans. Compare to endogenous production during exercise

There is no established "effective dose" of MOTS-c for humans yet; all use is experimental, and human data come mainly from an analog (CB4211) plus extrapolation from rodent studies and biohacker practice. What we can do is (1) outline the animal dose ranges and common human-style protocols and (2) compare those exposures to the transient endogenous rise from exercise. [\[25\]](#) [\[26\]](#) [\[27\]](#)

What we know about dosing

Preclinical dosing (mostly mice/rats, i.p. injection): [\[28\]](#) [\[29\]](#) [\[30\]](#) [\[31\]](#)

- Metabolic / insulin-sensitizing studies: 0.5–5 mg/kg/day for 8–12 weeks. [\[29\]](#) [\[31\]](#)
- Exercise-performance and mitochondrial function: 5–15 mg/kg/day for 2–3 weeks. [\[32\]](#) [\[33\]](#) [\[28\]](#) [\[29\]](#)
- Shock/infection models: single or short-course doses of 20–50 mg/kg around the insult. [\[25\]](#) [\[29\]](#)

A recent 2025 review of MOTS-c in disease models summarizes that: [\[29\]](#)

- Lower doses (0.5–5 mg/kg) are used for longer durations (8–12 weeks).
- Higher doses (10–15 mg/kg) are used for shorter courses (2–4 weeks).

If you translate the commonly used 5–15 mg/kg rodent range to a 70-kg human (using simple mg/kg, not body-surface correction, as many peptide clinics do in practice):

- 5 mg/kg \approx 350 mg/day
- 10 mg/kg \approx 700 mg/day
- 15 mg/kg \approx 1050 mg/day

These are far above what most “anti-aging” protocols actually use; they’re simply what the animal literature uses to clearly see effects.

Human-adjacent data (CB4211 analog):

- CB4211 (a MOTS-c analog) was given at 25 mg once-daily subcutaneous for 28 days in obese people with fatty liver and was generally safe but caused frequent persistent injection-site nodules. [\[26\]](#) [\[25\]](#)
- This is the only peer-reviewed human dosing-type anchor we have, and it is for an analog, not native MOTS-c. [\[26\]](#) [\[25\]](#)

Typical “clinic / biohacker” style regimens (non-trial, extrapolated):

These are not from controlled trials but compiled in secondary reviews and peptide-clinic guidance: [\[34\]](#) [\[35\]](#) [\[26\]](#)

- 5–10 mg subcutaneous 2–3 times per week, or
- 10–20 mg subcutaneous daily for 2–4 weeks, then off for several weeks.

You can think of these as micro-doses relative to the per-kg animal doses; they’re chosen empirically to balance cost, unknown risk, and convenience rather than being “equivalent” to rodent protocols.

Endogenous MOTS-c from exercise

In the key human exercise paper: [\[30\]](#) [\[27\]](#) [\[36\]](#) [\[28\]](#)

- Acute high-intensity exercise increased **MOTS-c in skeletal muscle ~11.9-fold** over pre-exercise levels (relative change). [\[27\]](#) [\[30\]](#)
- Circulating plasma MOTS-c rose **~1.5–1.6-fold during and after exercise**, then returned to baseline within about 4 hours. [\[28\]](#) [\[30\]](#) [\[27\]](#)

So, one hard comparison we can make:

Source	Approximate change in MOTS-c	Duration	Notes
Single bout of intense exercise	~11.9-fold in muscle; ~1.5–1.6-fold in plasma vs baseline [30] [27]	Peaks during/just after, back to baseline by ~4 h [30]	Endogenous production, tightly regulated.
Typical “clinic” MOTS-c protocol	5–20 mg per injection, 2–7×/week (empirical) [26] [34] [35]	Hours per injection; chronic over weeks	No good PK data; total exposure likely well above a single exercise-induced pulse.
Rodent performance studies	5–15 mg/kg/day i.p. [28] [29] [30]	2–3 weeks	Produces robust metabolic and performance effects; dosing much higher per kg than human biohacker practice.

We do **not** yet have good human pharmacokinetic data that say “X mg s.c. equals the same area-under-curve as Y minutes of high-intensity exercise,” so any equivalence is speculative. Mechanistically, exercise gives brief, large spikes in tissue, whereas injections give longer, pharmacologic exposures. [\[27\]](#) [\[25\]](#) [\[29\]](#)

How to interpret this for PGC-1 α / longevity use

- From a safety and physiology standpoint, repeated Zone-2 plus periodic higher-intensity efforts are the most proven way to upregulate MOTS-c and downstream AMPK–SIRT1–PGC-1 α signaling in humans. [\[37\]](#) [\[36\]](#) [\[28\]](#) [\[27\]](#)
- Exogenous MOTS-c in animals clearly improves metabolic flexibility and performance at 5–15 mg/kg, but the human-equivalent exposures are unknown, and long-term safety is untested. [\[31\]](#) [\[28\]](#) [\[29\]](#)
- If someone experiments, most longevity clinicians stay in the **single-digit to low-tens of milligrams per dose** range, a few times per week, i.e., much lower than the mg/kg doses used in rodents, precisely because we do not know the risk curve. [\[35\]](#) [\[34\]](#) [\[26\]](#)

In practice, the rational approach is to treat MOTS-c as an adjunct “amplifier” layered on top of a strong exercise program rather than as a replacement, and to keep doses conservative until proper human dose-finding studies exist.

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<q>5 mg/kg \approx 350 mg/day

10 mg/kg \approx 700 mg/day

15 mg/kg \approx 1050 mg/day</q> what are the HED doses

Using standard FDA allometric scaling (Reagan-Shaw method), the mouse-to-human Km ratio is $3/37 \approx 0.081$, so the human-equivalent dose (HED) is about 8.1% of the mouse mg/kg dose. [\[41\]](#)

Starting from your mouse doses:

- 5 mg/kg in mice \rightarrow HED $\approx 5 \times \frac{3}{37} \approx 0.41$ mg/kg.
 - For a 70-kg human: $0.41 \times 70 \approx 29$ mg/day.
- 10 mg/kg in mice \rightarrow HED $\approx 10 \times \frac{3}{37} \approx 0.81$ mg/kg.
 - For a 70-kg human: $0.81 \times 70 \approx 57$ mg/day.
- 15 mg/kg in mice \rightarrow HED $\approx 15 \times \frac{3}{37} \approx 1.22$ mg/kg.
 - For a 70-kg human: $1.22 \times 70 \approx 86$ mg/day.

So, roughly, your earlier “straight mg/kg” transliteration (350/700/1050 mg) corresponds to **allometrically corrected HEDs of ~30, ~60, and ~85 mg/day** for a 70-kg person.

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