MOTS-c — Research Summary

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1. What It Is

MOTS-c (mitochondrial open reading frame of the 12S rRNA type-c) is a 16-amino-acid mitochondrial-derived peptide (MDP) — a signaling peptide encoded within mitochondrial DNA rather than the cell nucleus, distinguishing it from most peptide hormones. It was identified as part of a broader class of mitochondrial-derived peptides that includes humanin.

- **Proposed mechanism:** MOTS-c is reported to move to the nucleus during metabolic stress and influence nuclear gene expression; its primary target tissue appears to be skeletal muscle, where it inhibits the folate cycle and de novo purine biosynthesis, leading to AMPK activation.

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2. Reported Effects in Research Literature

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Preclinical (well-established, all animal/in vitro): - The foundational 2015 *Cell Metabolism* paper reported MOTS-c treatment in mice enhanced glucose clearance and insulin sensitivity — a hyperinsulinemic-euglycemic clamp study found roughly a 30% increase in the glucose infusion rate required to maintain euglycemia during insulin stimulation, with the effect localized to skeletal muscle (via AMPK activation and increased GLUT4 expression) rather than the liver. - MOTS-c treatment prevented age-dependent and high-fat-diet-induced insulin resistance, as well as diet-induced obesity, in mouse models. - A 2023 review summarized broader research connections to skeletal muscle glucose metabolism, obesity, insulin resistance, aging, cardiovascular biology, and inflammation.

Human evidence — currently entering controlled trials: - Human research to date has been almost entirely observational: MOTS-c blood levels are reported to correlate with age and metabolic health, but this doesn’t establish that administering it would produce a treatment effect. - A registered Phase 2a trial (NCT07505745) is currently investigating investigational MOTS-c in adults with prediabetes and overweight/obesity, with the primary endpoint being change in OGTT-derived insulin sensitivity (Matsuda Index) over a 12-week double-blind treatment period. This is the first substantive human interventional trial of MOTS-c itself. - A related but distinct compound, CB4211 (a modified, lab-engineered MOTS-c analog developed by CohBar, not native MOTS-c), completed early-stage Phase 1a/1b human testing, with early results describing it as well tolerated, with some shifts in liver enzymes and blood sugar noted.

Research limitation to note: As of 2026, there is no completed, published human treatment trial for native MOTS-c itself — the current Phase 2a study (NCT07505745) is the first, and is still recruiting/ongoing. Existing human data is observational (correlation, not intervention).

PCAC update (July 23, 2026): The FDA’s Pharmacy Compounding Advisory Committee voted 7–5 (two abstentions) to recommend MOTS-c for inclusion on the 503A Bulk Drug Substances List, overriding FDA staff’s own recommendation against inclusion. This is a non-binding advisory recommendation only — it does not add MOTS-c to the list, does not authorize compounding, and does not change RUO sale status. A formal rulemaking process, expected to take 8–12 months, would be required before any actual change takes effect.

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3. Clinical & Preclinical Study References

- Lee C, et al. “The mitochondrial-derived peptide MOTS-c promotes metabolic homeostasis and reduces obesity and insulin resistance.” *Cell Metabolism.* 2015. PMID: 25738459 — Full text
- Review: “MOTS-c: a promising mitochondrial-derived peptide for therapeutic exploitation.” *Frontiers in Endocrinology.* 2023. PMC9905433
- Kim KH, et al. “The mitochondrial-derived peptide MOTS-c is a regulator of plasma metabolites and enhances insulin sensitivity.” *Physiological Reports.* 2019. PMC6640593
- Current Phase 2a human trial: NCT07505745 — MOTS-c for Improving Insulin Sensitivity in Adults With Prediabetes and Overweight/Obesity

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4. Reconstitution Process

For research/laboratory handling purposes only.

Keep out of reach of children. Not for use by pregnant or nursing individuals. For laboratory research use by qualified personnel only.

1. **Materials needed:** lyophilized (freeze-dried) MOTS-c powder, bacteriostatic water, alcohol swabs, syringe with needle.
2. **Bring the vial to room temperature** before reconstitution.
3. **Sanitize** the rubber stopper of both vials with an alcohol swab.
4. **Add the water slowly** down the *inside wall* of the vial, to reduce shear/foaming.
5. **Do not shake.** Gently swirl or roll between palms until fully dissolved.
6. **Inspect the solution** — should be clear and free of particulates.
7. **Label the vial** with reconstitution date and concentration.
8. **Storage:** refrigerate (2–8°C); avoid freeze-thaw cycles.

Reference: Bacteriostatic Water Volume by Vial Size

Vial Size	BAC Water Added	Resulting Concentration
5 mg	1 mL	5 mg/mL
5 mg	2 mL	2.5 mg/mL
5 mg	5 mL	1 mg/mL
10 mg	1 mL	10 mg/mL
10 mg	2 mL	5 mg/mL
10 mg	4 mL	2.5 mg/mL
10 mg	5 mL	2 mg/mL
10 mg	10 mL	1 mg/mL
40 mg	4 mL	10 mg/mL
40 mg	8 mL	5 mg/mL

Notes: Your order sheet also carries a 40mg MOTS-c vial size, included above. Higher water volume = more dilute solution; lower volume = more concentrated. Always use bacteriostatic water (0.9% benzyl alcohol) for multi-draw vials; sterile water without preservative should be discarded within 24 hours.

Document created: July 16, 2026. **Revision 1:** July 29, 2026. Regulatory status (FDA compounding lists, WADA lists) is actively shifting; re-verify against current sources before any customer-facing use.
