

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.

2. Reported Effects in Research Literature

- 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, localized to skeletal muscle via AMPK activation and increased GLUT4 expression.
- MOTS-c treatment prevented age-dependent and high-fat-diet-induced insulin resistance, as well as diet-induced obesity, in mouse models.
- A February 2026 cell-biology study (UCLouvain and Aspetar, published in Physiological Reports) examined MOTS-c and humanin against dexamethasone-induced atrophy in human skeletal muscle cells — adding to a growing body of in-vitro human-cell data even as in-vivo human trial data lags behind.
- Two additional 2026 mechanistic papers: a Free Radical Biology and Medicine study reported MOTS-c targets SLC7A11 to preserve spermatogenesis by suppressing ferroptosis (an iron-dependent form of cell death) in an animal model; a separate 2026 Autophagy paper reported MOTS-c improved ischemic soft-tissue flap survival in an animal model by reducing lysosomal membrane permeability and endothelial pyroptosis.
- 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 and is still recruiting/ongoing.
- 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, described as well tolerated with some shifts in liver enzymes and blood sugar noted.
- As of 2026, there is no completed, published human treatment trial for native MOTS-c itself. Existing human data is observational (correlation, not intervention).
- MOTS-c is prohibited at all times in competitive sport under the World Anti-Doping Agency's S4 category (hormone and metabolic modulators; WADA identifies it among AMPK activators).
- 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.

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

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

UCLouvain/Aspetar. MOTS-c and humanin vs. dexamethasone-induced atrophy in human skeletal muscle cells. Physiological Reports. 2026.

MOTS-c targets SLC7A11 to preserve spermatogenesis by suppressing ferroptosis. Free Radic Biol Med. 2026. PMID: 41933740

MOTS-c improves ischemic soft tissue flap survival by reducing lysosomal membrane permeability and endothelial pyroptosis. Autophagy. 2026. PMID: 42153537

Regulatory/Safety Note: MOTS-c is not approved by the FDA for the diagnosis, treatment, cure, or prevention of any disease.

Verification Update: Three new 2026 preclinical/mechanistic papers were identified and added: a human-skeletal-muscle-cell atrophy study (UCLouvain/Aspetar) and two animal-model mechanistic papers (spermatogenesis/ferroptosis; ischemic flap survival). None constitute human treatment-outcome data — the core conclusion (no completed human efficacy trial for native MOTS-c) is unchanged.

This compound has not been evaluated by the FDA and is not intended to diagnose, treat, cure, or prevent any disease in humans or animals.

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