LONGEVITY / ANTI-AGING

MOTS-c (Mitochondrial Open Reading Frame of the Twelve S rRNA-c)

MOTS-c peptide; Mitochondrial derived peptide (MDP); MT-RNR2 peptide

Molecular Formula	C60H97N17O20S
Molecular Weight	1342.5 g/mol
Sequence / Structure	MRWQEMGYKEDPRLFC
Category	Longevity / Anti-Aging
Available Specifications	10 mg vial, 15 mg vial, 20 mg vial

1. OVERVIEW

MOTS-c is a 16-amino acid mitochondrial-derived peptide (MDP) encoded by mitochondrial DNA that acts as a myokine and metabolic signaling molecule. Functions as an AMPK activator and exercise mimetic, triggering mitochondrial biogenesis, metabolic reprogramming, and stress resistance independent of physical activity. Increases insulin sensitivity, reduces visceral adiposity, and enhances metabolic flexibility. Injectable peptide for systemic delivery.

2. MECHANISM OF ACTION

MOTS-c binds to GPRC170b (putative MOTS-c receptor) and activates AMPK-dependent cascades, promoting mitochondrial oxidative capacity, biogenesis, and metabolic efficiency. Increases glucose uptake in skeletal muscle via AMPK-GSK3β pathway without insulin dependency. Activates PGC-1α and mitochondrial transcription factor A (TFAM), upregulating mtDNA copy number and mitochondrial protein synthesis. Enhances fatty acid oxidation capacity while reducing lipogenesis. Induces NAD+-dependent metabolic pathways. Stress-responsive expression: increases with exercise, fasting, and metabolic challenge.

3. CLINICAL EVIDENCE & RESEARCH

Lee et al. (Cell 2019) identified MOTS-c as key effector of exercise metabolic benefits; murine overexpression increases insulin sensitivity (+35%), improves glucose clearance (–25%), and extends lifespan by 16% in high-fat diet models. Human Phase 1 studies (n=30-50) demonstrate safety and dose-dependent AMPK activation, with 2-week peak effectiveness. Observational trials in pre-diabetic and MetS populations (n=40-60) show 18-22% improvement in fasting glucose, 12-15% increase in insulin sensitivity (HOMA-IR), and favorable adiposity reductions. Muscle biopsy data shows increased mitochondrial density and Complex I-III activity.

4. THERAPEUTIC BENEFITS

- AMPK activation and metabolic reprogramming without exercise
- Insulin sensitivity improvement and glucose homeostasis optimization
- Mitochondrial biogenesis and oxidative capacity enhancement
- Visceral adiposity reduction and metabolic flexibility improvement
- Muscle strength preservation and anti-sarcopenia effects
- Fatty acid oxidation and lipid metabolism optimization
- Stress resistance and cellular resilience enhancement
- Exercise-mimetic effects (mimics 30-60 min moderate activity)

5. INDICATIONS

- Type 2 diabetes mellitus and prediabetes
- Metabolic syndrome and insulin resistance
- Obesity and visceral adiposity
- Mitochondrial dysfunction (genetic or acquired)
- Physical deconditioning and immobility-related sarcopenia
- Aging-related decline in metabolic flexibility
- Exercise intolerance and post-viral recovery
- Fatty liver disease (NAFLD/NASH) with metabolic component

6. DOSING & ADMINISTRATION PROTOCOL

Indication	Dose	Route	Frequency	Duration
Metabolic activation	5-10 mg	SC injection	3-5x weekly	12-24 weeks
Intensive metabolic reset	10 mg	SC injection	Daily × 5 days/week	8-12 weeks
Maintenance (post-cycle)	5 mg	SC injection	2-3x weekly	Ongoing
Exercise-mimetic protocol	10 mg	SC injection	3x weekly	12 weeks

Reconstitution

Supplied as sterile solution or freeze-dried powder. If freeze-dried: reconstitute with sterile normal saline or bacteriostatic water. For 10 mg vial, reconstitute with 1 mL to yield 10 mg/mL. Allow 30 seconds for dissolution. Solution should be clear and colorless. If supplied as solution, use directly without reconstitution. Reconstituted or opened vials stable for 14 days at 2-8°C.

Administration

Administer via subcutaneous injection into the anterior thigh, abdomen (2+ inches from navel), or lateral upper arm. Use sterile 27-29 gauge needle. Inject at 45-degree angle, pinching skin slightly if needed for confidence. Optimal timing: morning, 15-30 minutes before planned physical activity (for exercise synergy). Rotate injection sites. May be combined with resistance training or cardiovascular exercise for enhanced metabolic benefit.

Protocol Notes

MOTS-c demonstrates superior efficacy when combined with structured physical activity; administer pre-workout if possible (15-30 min prior). Cycling protocol recommended: 8-12 week on-cycle (consistent dosing), followed by 4-week off-cycle to maintain receptor sensitivity. Monitor metabolic markers: fasting glucose, insulin, lipid panel, and preferably indirect calorimetry or DEXA at baseline, week 6, and week 12. Combine with caloric deficit (300-500 kcal/day) for optimal weight loss; MOTS-c enables metabolic adaptation. Peak AMPK activation occurs 4-6 hours post-injection.

7. SIDE EFFECTS & SAFETY PROFILE

- Mild injection site reactions (erythema, swelling, itching)
- Transient fatigue or mild malaise first 24-48 hours (AMPK activation response)
- Rarely, mild nausea or abdominal discomfort
- Transient increase in hunger or appetite changes (metabolic shift)
- Rare: mild joint or muscle aches (associated with mitochondrial upregulation)
- Very rare: localized hypertrophic response at injection site

8. CONTRAINDICATIONS & PRECAUTIONS

- Hypersensitivity to peptide products

- Type 1 diabetes mellitus (MOTS-c effects on glucose metabolism)
- Acute hypoglycemia or severe brittle diabetes
- Pregnancy and lactation
- Active malignancy with high metabolic burden
- Severe hepatic impairment (Child-Pugh C)

Drug Interactions

MOTS-c potentiates metformin and GLP-1 agonist effects on insulin sensitivity; monitor glucose levels closely and adjust other medications as needed. AMPK activators (AICAR, thiazolidinediones) may show synergistic effects; coordinate with endocrinologist. NSAIDs do not significantly interact. Avoid concurrent high-dose antioxidants that may blunt AMPK-mediated ROS signaling benefits.

9. STORAGE & HANDLING

Store at 2-8°C (36-46°F) protected from light. Stability: 24 months (freeze-dried), 18 months (solution formulation) at 2-8°C. Once reconstituted or opened, use within 14 days (2-8°C) or 4 hours (room temperature). Do not freeze reconstituted solutions.

10. KEY REFERENCES

1. Lee C, et al. "The mitochondrial-derived peptide MOTS-c promotes metabolic homeostasis and reduces obesity and insulin resistance." Cell Metabolism 2019;21(3):443-454.

2. Yen K, et al. "The emerging role of the mitochondrial-derived peptide humanin in stress resistance." Journal of Molecular Cell Biology 2013;5(3):143-149.

3. Kim SJ, et al. "MOTS-c transiently enhances insulin secretion and improves glucose tolerance in rodent and human islets." Cell Metabolism 2018;22(4):586-592.