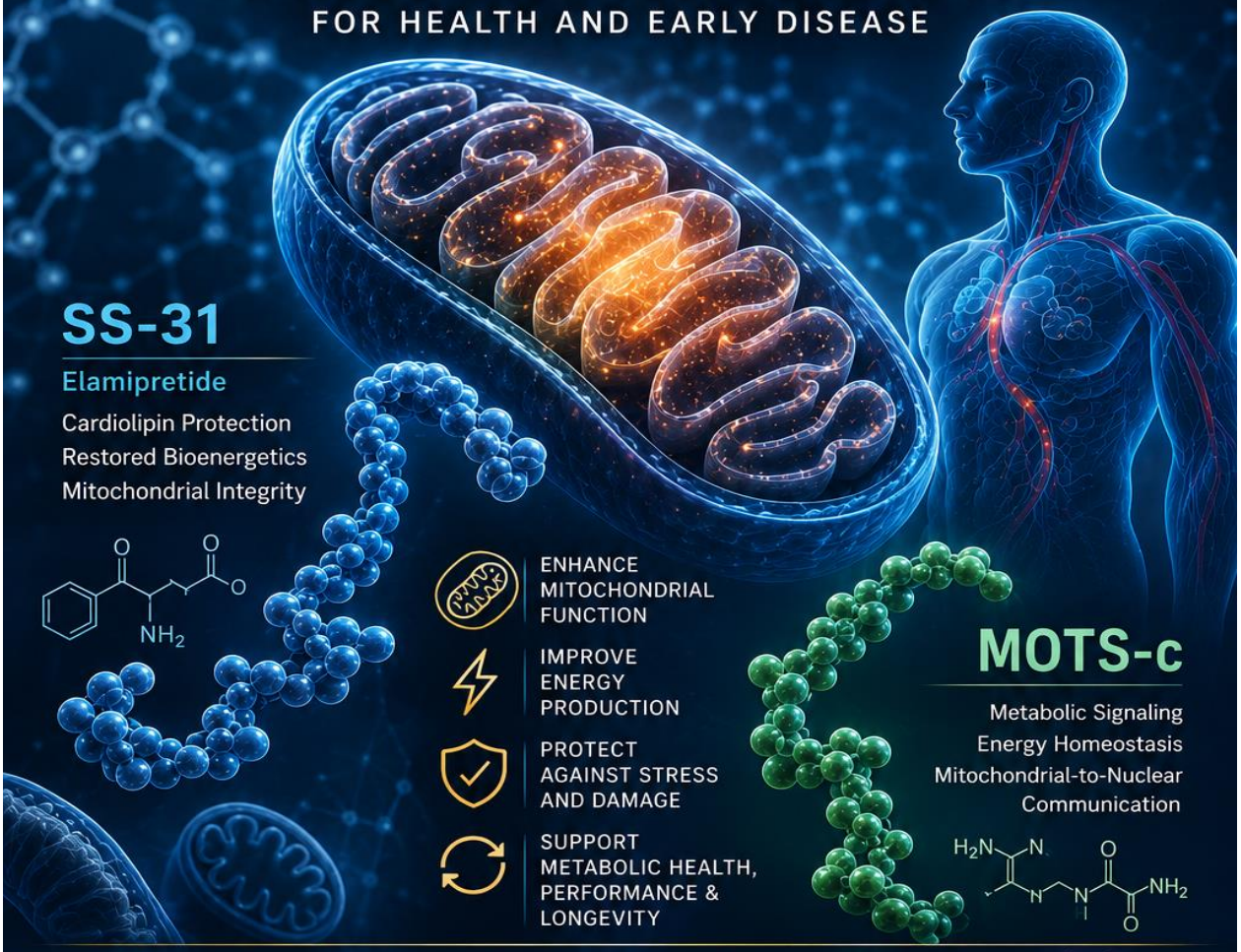
PEPTIDES FOR HEALTH

SS-31 & MOTS-c

TARGETING MITOCHONDRIA. OPTIMIZING HEALTH.

MECHANISMS • PROTOCOLS • APPLICATIONS
FOR HEALTH AND EARLY DISEASE



SS-31

Elamipretide

Cardiolipin Protection
Restored Bioenergetics
Mitochondrial Integrity

- ENHANCE MITOCHONDRIAL FUNCTION
- IMPROVE ENERGY PRODUCTION
- PROTECT AGAINST STRESS AND DAMAGE
- SUPPORT METABOLIC HEALTH, PERFORMANCE & LONGEVITY

MOTS-c

Metabolic Signaling
Energy Homeostasis
Mitochondrial-to-Nuclear Communication

NEUROPROTECTION | CARDIOVASCULAR SUPPORT | RENAL & METABOLIC HEALTH | PERFORMANCE & RECOVERY | HEALTHSPAN & LONGEVITY

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MILLENNIUM HEALTH CENTERS
Addressing Health One Neuron at a Time®

Introduction: SS-31 and MOTS-c

A Complementary Approach to Mitochondrial Function and ATP Optimization

Mitochondria are the principal energy-generating organelles of the human cell, converting nutrients into adenosine triphosphate (ATP) through the coordinated processes of the tricarboxylic acid cycle, electron transport, and oxidative phosphorylation. ATP provides the immediately usable energy required for virtually every energy-dependent cellular process, including membrane transport, protein synthesis, muscle contraction, neuronal signaling, cellular repair, and maintenance of ionic gradients. Consequently, the ability of mitochondria to efficiently generate ATP is fundamental not only to survival but also to physical performance, cognitive function, metabolic health, tissue recovery, and healthy aging.

Mitochondrial performance, however, is not determined simply by the number of mitochondria present within a cell. Optimal energy production requires preservation of the inner mitochondrial membrane, appropriate organization of the electron transport chain, maintenance of the mitochondrial membrane potential, adequate substrate availability, controlled production of reactive oxygen species, and the ability of the mitochondria to adapt to changing cellular energy requirements. Disturbances at any of these levels can decrease the efficiency with which oxygen and metabolic substrates are converted into ATP.

Two peptides of particular interest in mitochondrial biology are SS-31 (elamipretide) and MOTS-c. Although both influence mitochondrial function, they operate through distinctly different biological mechanisms. This distinction is important because their actions may be viewed as potentially complementary rather than redundant.

SS-31: Supporting the Mitochondrial Energy-Producing Machinery

SS-31, also known as elamipretide, is a mitochondria-targeting tetrapeptide (4 amino acids in length) with a particular affinity for the inner mitochondrial membrane. A major component of its biological activity involves interactions with cardiolipin, a specialized phospholipid highly concentrated within this membrane.

Cardiolipin plays a critical structural and functional role in mitochondrial bioenergetics. It contributes to the organization of mitochondrial cristae and supports proteins and protein complexes involved in electron transport and oxidative phosphorylation. When cardiolipin becomes damaged or its interactions with mitochondrial proteins are disturbed, electron transfer may become less efficient, oxidative stress may increase, and ATP production may decline.

SS-31 interacts with cardiolipin and influences the relationship between cardiolipin and cytochrome c. Experimental studies demonstrate that this interaction can preserve cytochrome c's electron-transfer function, improve mitochondrial respiration, and increase the efficiency of ATP synthesis.

The mechanism is therefore considerably more sophisticated than simply describing SS-31 as an antioxidant. Contemporary research indicates that elamipretide influences mitochondrial membrane properties and cardiolipin-dependent proteins central to mitochondrial physiology and bioenergetics.

This provides a useful conceptual description:

SS-31 helps optimize the mitochondrial machinery responsible for producing ATP.

Importantly, this concept is supported by human evidence. In a randomized, double-blind, placebo-controlled study involving older adults with impaired mitochondrial function, a single administration of elamipretide produced a measurable improvement in skeletal-muscle mitochondrial energetic capacity, including ATPmax.

MOTS-c: Regulating Metabolic Adaptation and Energy Utilization

MOTS-c approaches mitochondrial optimization from a very different direction.

MOTS-c is a **16-amino-acid** mitochondrial-derived peptide encoded within the mitochondrial 12S rRNA region. Rather than functioning primarily as a structural protector of the inner mitochondrial membrane, MOTS-c behaves as a metabolic signaling molecule that participates in communication between mitochondrial energetic status and cellular metabolism.

One of its most important signaling pathways involves AMP-activated protein kinase (AMPK), a major cellular energy sensor. Experimental work indicates that MOTS-c influences the folate cycle and de novo purine biosynthesis, resulting in accumulation of AICAR and activation of AMPK. Through these and related pathways, MOTS-c has been associated with regulation of glucose utilization, insulin sensitivity, metabolic flexibility, skeletal-muscle metabolism, and cellular adaptation to energetic stress.

MOTS-c possesses another particularly intriguing characteristic. Under metabolic or oxidative stress, it can translocate into the cell nucleus, where it participates in the regulation of nuclear gene expression. This response is AMPK-dependent and includes interaction with stress-responsive pathways involving NRF2 and antioxidant-response elements.

MOTS-c therefore represents an important example of mitochondrial-to-nuclear communication: mitochondria are not merely responding to instructions from the nucleus; they can generate signals that help modify nuclear responses to cellular energy requirements and environmental stress.

A useful conceptual description is therefore:

MOTS-c helps the cell sense, regulate, and adapt to changing metabolic and energetic demands.

Two Different Approaches to Mitochondrial Optimization

The biological distinction between these peptides provides the rationale for considering them together.

SS-31 → MITOCHONDRIAL STRUCTURE & BIOENERGETICS

Cardiolipin interaction
↓
Inner mitochondrial membrane/cristae organization
↓
Electron transport efficiency
↓
Oxidative phosphorylation
↓
ATP production

Whereas:

MOTS-c → METABOLIC SIGNALING & ADAPTATION

Cellular energetic/metabolic stress
↓
Folate-AICAR signaling
↓
AMPK activation
↓
Metabolic and stress-response signaling
↓
Mitochondrial-to-nuclear communication
↓
Improved cellular energy homeostasis and adaptation

This distinction suggests a potentially complementary strategy: SS-31 targets components of the machinery responsible for generating mitochondrial energy, whereas MOTS-c influences the signaling systems that regulate how cells respond to and manage energetic demand.

In simplified terms:

SS-31 helps the mitochondria produce energy efficiently.

MOTS-c helps the cell regulate and adapt its use of energy.

Optimizing ATP Production

The objective of mitochondrial optimization should not simply be to force mitochondria to manufacture progressively greater quantities of ATP. Healthy mitochondrial function requires the ability to match ATP production to cellular demand while minimizing unnecessary oxidative and metabolic stress.

This concept is particularly important because ATP production and reactive oxygen species generation are intimately associated with electron transport. Improving mitochondrial efficiency may therefore be more physiologically desirable than indiscriminately increasing mitochondrial activity.

From this perspective, SS-31 and MOTS-c address two complementary components of mitochondrial optimization.

SS-31 may support the structural and bioenergetic environment required for efficient oxidative phosphorylation, while MOTS-c may support metabolic flexibility, cellular stress adaptation, and energy-sensing pathways that determine when and how metabolic resources are utilized. Research on MOTS-c consistently links the peptide to energy metabolism, AMPK signaling, stress homeostasis, and adaptive responses.

This provides the biological rationale for a RESTORE → ACTIVATE/ADAPT model:

RESTORE — SS-31
Support mitochondrial membrane organization, electron transport, oxidative phosphorylation, and ATP-generating efficiency.

ACTIVATE/ADAPT — MOTS-c

Support metabolic signaling, AMPK activity, cellular energy sensing, stress adaptation, and mitochondrial-to-nuclear communication.

The combination is therefore scientifically interesting because it approaches mitochondrial performance from two different levels of cellular biology rather than attempting to accomplish the same function with two different compounds.

From Mitochondrial Dysfunction to Mitochondrial Optimization

Much of the scientific literature surrounding mitochondrial therapeutics appropriately focuses on disease states characterized by impaired bioenergetics. However, the same fundamental pathways, electron transport, oxidative phosphorylation, metabolic flexibility, redox balance, and mitochondrial signaling, also determine mitochondrial performance in otherwise healthy individuals.

This has generated considerable interest in whether mitochondrial-directed interventions might eventually have applications beyond treatment of established mitochondrial dysfunction and toward preservation or optimization of mitochondrial performance during aging, exercise, metabolic stress, recovery, and periods of increased energetic demand.

That possibility remains an emerging area of investigation.

The evidence supporting SS-31 is considerably more clinically developed than that supporting MOTS-c. Human studies have demonstrated biological effects of elamipretide on mitochondrial energetics, whereas much of the therapeutic evidence for MOTS-c remains derived from cellular and animal models. Furthermore, there is presently no established controlled human clinical trial demonstrating that combined SS-31 and MOTS-c therapy increases ATP production or improves performance in healthy adults.

Accordingly, the proposed use of these peptides together for mitochondrial optimization should be regarded as a translational and investigational strategy derived from their complementary mechanisms of action, rather than an established standard of medical care.

Nevertheless, the underlying biology presents a compelling model:

Protect the mitochondrial environment.
Improve electron transport efficiency.
Support oxidative phosphorylation.
Enhance cellular energy sensing.
Promote metabolic adaptation.
Optimize, not simply maximize, ATP production.

Within this framework, SS-31 and MOTS-c represent two distinctly different approaches to one fundamental objective: maintaining the ability of the mitochondria to efficiently generate, regulate, and deliver the energy required for optimal cellular function.

Mechanism of Action: SS-31 (Elamipretide)

SS-31, also known as **elamipretide**, is a synthetic mitochondria-targeting tetrapeptide designed to influence mitochondrial structure and bioenergetic function at the level of the **inner mitochondrial membrane (IMM)**. Unlike conventional antioxidants that primarily attempt to neutralize reactive oxygen species after they have been generated, SS-31 appears to act more fundamentally by modifying the mitochondrial membrane environment in which electron transport and oxidative phosphorylation occur.

This distinction is central to understanding SS-31. Its biological effects appear to arise from several interconnected mechanisms involving **cardiolipin, membrane electrostatics, respiratory-chain organization, cytochrome c, ATP production, redox balance, and mitochondrial protein interactions**.

Targeting the Inner Mitochondrial Membrane

SS-31 is a small, water-soluble tetrapeptide composed of alternating aromatic and positively charged amino-acid residues. These physicochemical characteristics allow it to cross cellular membranes and preferentially associate with mitochondrial membranes without requiring the very large mitochondrial membrane potential typically used by other mitochondria-targeting compounds.

Once within the mitochondrion, SS-31 concentrates at the **inner mitochondrial membrane**, the location of the electron transport chain and ATP synthase.

This positioning is particularly important because the inner mitochondrial membrane is not merely a barrier separating mitochondrial compartments. It is the functional platform upon which oxidative phosphorylation occurs.

The membrane folds inward to form **cristae**, dramatically increasing the surface area available for the respiratory complexes and ATP-producing machinery. Consequently, disruption of inner-membrane architecture can directly compromise mitochondrial energy production. Contemporary mechanistic studies continue to identify the IMM as the primary site of SS-31 activity.

Cardiolipin: A Central Component of SS-31 Activity

One of the most extensively characterized interactions of SS-31 is with **cardiolipin**.

Cardiolipin is an unusual phospholipid found predominantly within the inner mitochondrial membrane. Its **four fatty-acid chains** and highly anionic head group give it structural properties that distinguish it from most other membrane phospholipids.

Cardiolipin contributes to several processes essential for mitochondrial function:

Cristae architecture

Electron transport chain organization

Respiratory supercomplex stability

Cytochrome c function

ATP synthase organization

Mitochondrial membrane dynamics

Apoptotic signaling

Because of these functions, cardiolipin can be viewed as an important structural organizer of mitochondrial bioenergetics.

SS-31 associates strongly with cardiolipin-containing membranes. More recent work suggests that the consequences of this interaction extend beyond simply "protecting cardiolipin." SS-31 can alter membrane electrostatics and lipid packing and influence cardiolipin-dependent protein organization within the inner mitochondrial membrane.

Preservation of Cristae Architecture

The folds of the inner mitochondrial membrane, **mitochondrial cristae,** contain much of the machinery responsible for oxidative phosphorylation.

Healthy cristae provide an organized environment in which electrons move through respiratory complexes I through IV, establishing the proton gradient ultimately utilized by Complex V (ATP synthase) to generate ATP.

Mitochondrial injury can disrupt this architecture.

Alterations in cardiolipin composition, lipid oxidation, membrane organization, or respiratory-protein interactions can destabilize cristae and decrease the efficiency of oxidative phosphorylation.

By interacting with the cardiolipin-rich inner membrane, SS-31 appears capable of improving membrane organization and supporting the assembly and function of cardiolipin-dependent mitochondrial proteins. Contemporary reviews therefore increasingly describe SS-31 as a **mitochondrial membrane-modifying and bioenergetic peptide**, rather than simply an antioxidant.

Cytochrome c and Electron Transport

Cytochrome c occupies an important position within mitochondrial energy production.

Under physiological conditions, cytochrome c transfers electrons from **Complex III to Complex IV** of the electron transport chain.

Cardiolipin helps position and regulate cytochrome c at the inner mitochondrial membrane. Under conditions of mitochondrial injury or excessive oxidative stress, however, the cardiolipin–cytochrome c interaction can change. Cytochrome c can acquire peroxidase activity, promoting cardiolipin oxidation and contributing to mitochondrial membrane damage.

SS-31 appears to favorably influence this cardiolipin–cytochrome c relationship.

The result is preservation of cytochrome c's electron-transfer function while reducing processes associated with cardiolipin peroxidation.

Conceptually:

SS-31 → Cardiolipin interaction → Improved cytochrome c environment → More efficient electron transfer → Improved oxidative phosphorylation

This mechanism provides an important connection between SS-31's membrane effects and its ability to influence mitochondrial energy production.

Organization of the Electron Transport Chain

The respiratory complexes of the electron transport chain do not necessarily function as completely isolated molecular structures. They can associate into larger assemblies commonly referred to as **respiratory supercomplexes**.

Cardiolipin contributes to the organization and stability of these complexes.

SS-31 appears to influence this environment by modifying cardiolipin-dependent membrane properties and interacting with proteins associated with oxidative phosphorylation.

Proteomic studies examining mitochondrial binding partners of SS-31 identified interactions with proteins involved in **oxidative phosphorylation and ATP production**, many of which are themselves cardiolipin-binding proteins.

This suggests that SS-31 may help improve the molecular environment in which electrons are transferred through the respiratory chain.

Greater efficiency of electron movement potentially means:

More effective proton pumping

↓

Better maintenance of the proton-motive force

↓

Improved ATP synthase activity

↓

Greater efficiency of ATP production

Improving Oxidative Phosphorylation and ATP Production

The ultimate energetic consequence of these mitochondrial effects is the potential improvement of **oxidative phosphorylation**.

During oxidative phosphorylation, electrons derived from metabolic substrates move through the electron transport chain. The energy released drives protons from the mitochondrial matrix into the intermembrane space.

This creates an electrochemical proton gradient.

ATP synthase then allows protons to flow back into the mitochondrial matrix and uses that stored electrochemical energy to convert:

ADP + Pi → ATP

SS-31 does not appear to function as a conventional metabolic stimulant that simply forces mitochondria to consume more substrate.

Instead, the evidence suggests that it can improve the **efficiency of the mitochondrial machinery responsible for oxidative phosphorylation**.

This distinction is important.

The objective is not simply:

MORE MITOCHONDRIAL ACTIVITY

but rather:

MORE EFFICIENT MITOCHONDRIAL ACTIVITY

Human evidence provides support for this concept. In a randomized placebo-controlled study of older adults selected for impaired mitochondrial function, a single dose of elamipretide increased the measured maximal mitochondrial ATP-production capacity (**ATPmax**) relative to placebo.

Thus, the mechanistic effects observed in experimental models have at least some measurable human bioenergetic correlate.

Improved ADP Sensitivity

Another important development in understanding SS-31 involves **ADP sensitivity**.

Mitochondria must sense cellular energy requirements. When ATP is consumed, ADP increases and becomes available to the mitochondria for conversion back into ATP.

Aging and mitochondrial dysfunction can impair the mitochondrial response to ADP.

Experimental work indicates that SS-31 can improve mitochondrial sensitivity to ADP, potentially involving the **adenine nucleotide translocator (ANT)** and other proteins responsible for transporting ADP and ATP across the inner mitochondrial membrane.

This is highly relevant to mitochondrial optimization because it suggests SS-31 may influence not only the machinery generating ATP but also the system controlling the availability of the substrate required for ATP synthesis.

The process can therefore be represented as:

Cell consumes ATP

↓

ATP → ADP

↓

ADP enters mitochondrial matrix

↓

Electron transport generates proton gradient

↓

ATP synthase phosphorylates ADP

↓

ATP returns to cytoplasm

↓

Cellular energy restored

SS-31 may improve the efficiency of several components within this cycle.

Reduction of Electron Leak and Oxidative Stress

Reactive oxygen species are normal products of mitochondrial respiration. At physiological concentrations, ROS also function as signaling molecules.

Problems arise when electron transport becomes inefficient.

Electrons can prematurely escape the respiratory chain and react with oxygen, producing excessive superoxide and other reactive oxygen species.

This creates a potentially self-amplifying cycle:

Mitochondrial dysfunction

↓

Electron leak

↓

Excess ROS

↓

Cardiolipin and membrane damage

↓

Further respiratory-chain dysfunction

↓

More ROS

SS-31 may help interrupt this cycle by improving the structural and functional environment of the electron transport chain.

Therefore, reductions in oxidative stress associated with SS-31 should not be attributed exclusively to direct radical scavenging. Current mechanistic evidence favors a broader explanation in which **improved mitochondrial membrane organization and bioenergetic efficiency reduce the conditions responsible for excessive ROS generation in the first place**.

This represents an important evolution from the original description of SS-31.

Membrane Electrostatics and Calcium Handling

Another emerging mechanism involves the electrical properties of the mitochondrial membrane itself.

SS-31 can alter the **surface electrostatic properties of mitochondrial membranes** without disrupting membrane integrity.

These changes may influence the distribution of ions and proteins near the membrane surface.

Experimental work has demonstrated that SS-31 can modify calcium distribution at the membrane interface and reduce the energetic burden associated with mitochondrial calcium stress.

This may be particularly relevant in tissues with high energetic and calcium-handling requirements, including:

1. Brain
2. Heart
3. Skeletal muscle
4. Kidney

These are also tissues particularly vulnerable to mitochondrial dysfunction because of their substantial ATP requirements.

PLSCR3: An Emerging Biological Target

An important development occurred in 2024 when a genome-wide CRISPR screen identified **phospholipid scramblase 3 (PLSCR3)** as an essential mediator of SS-31's mitochondrial protective effects in experimental kidney models.

Investigators demonstrated that SS-31 directly interacted with an N-terminal region of PLSCR3 and stimulated its phospholipid-scramblase activity. Loss of PLSCR3 abolished the protective effect of SS-31 in experimental models of acute kidney injury.

This finding expands the mechanism considerably.

The traditional model:

SS-31 → Cardiolipin

is increasingly becoming:

SS-31 → Inner mitochondrial membrane
↓
Cardiolipin + membrane electrostatics + cardiolipin-dependent proteins + PLSCR3
↓
Improved membrane organization
↓
Improved respiratory-chain function
↓
Improved mitochondrial bioenergetics

The relative importance of PLSCR3 across different human tissues and disease states remains under investigation, but the discovery provides an important additional molecular target through which SS-31 may exert its effects.

SS-31 as a Mitochondrial Bioenergetic Optimizer

Taken together, the evidence supports a multidimensional mechanism of action.

SS-31 appears capable of influencing:

Cardiolipin-associated membrane organization

Cristae architecture

Cytochrome c function

Respiratory-chain protein organization

Electron-transfer efficiency

ADP/ATP handling

Oxidative phosphorylation

Mitochondrial membrane electrostatics

ROS generation and redox balance

PLSCR3-dependent mitochondrial protection

These mechanisms converge upon a common physiological objective:

Improving the efficiency with which mitochondria convert metabolic energy into usable cellular ATP while maintaining mitochondrial structural integrity.

This is why SS-31 can appropriately be conceptualized as the **RESTORE** component of a proposed SS-31/MOTS-c mitochondrial strategy.

SS-31 primarily addresses the **mitochondrial energy-producing environment**, whereas MOTS-c operates more prominently through **cellular energy sensing, AMPK signaling, metabolic adaptation, and mitochondrial-to-nuclear communication**.

The distinction provides the mechanistic basis for considering a sequential approach:

SS-31

RESTORE
↓
Stabilize the mitochondrial environment
↓
Improve electron transport
↓
Improve oxidative phosphorylation
↓
Optimize ATP-generating capacity

followed by

MOTS-c

ACTIVATE & ADAPT
↓

AMPK and metabolic signaling
↓
Improve metabolic flexibility
↓
Coordinate mitochondrial–nuclear responses
↓
Adapt cellular metabolism to energetic demand

Thus, SS-31 should not simply be viewed as another antioxidant peptide. Current evidence supports a broader role as a mitochondrial membrane and bioenergetic modulator whose actions converge on improving the structural and functional efficiency of oxidative phosphorylation and ATP production.

Suggested pattern: SS-31 → then MOTS-c

Phase	Peptide	Suggested pattern	Purpose
1. Mitochondrial restoration	SS-31	Daily for approximately 4–8 weeks. (10mg-40mg)	Improve mitochondrial membrane/cardiolipin function and oxidative phosphorylation
2. Transition	SS-31 + MOTS-c	Introduce MOTS-c during approximately weeks 5–8 while continuing SS-31.	Begin metabolic signaling while mitochondrial function is being restored
3. Metabolic optimization	MOTS-c	Continue after SS-31 cycle; commonly used intermittently rather than continuously.	AMPK/metabolic signaling, glucose utilization, exercise adaptation and mitochondrial biogenesis
4. Maintenance/reassessment	—	Reassess symptoms and metabolic/mitochondrial markers before another cycle	Determine whether another SS-31 cycle, MOTS-c cycle, or neither is warranted

Why SS-31 first

The two peptides work at substantially different levels.

SS-31 → mitochondrial machinery. Elamipretide interacts with cardiolipin in the inner mitochondrial membrane, influencing membrane organization and mitochondrial energetics. Unlike MOTS-c, SS-31 now has substantial human exposure data and, since September 2025, an FDA-approved formulation (Forzinity) for Barth syndrome. The approved Barth-syndrome regimen is 40 mg SC once daily, although that should *not* be interpreted as an approved dose for general mitochondrial optimization. Clinical mitochondrial-disease studies have likewise generally used daily administration.

MOTS-c → mitochondrial signaling. MOTS-c is better conceptualized as a metabolic signaling peptide. Its experimental effects involve AMPK and cellular stress-response pathways and appear particularly relevant to metabolic flexibility, glucose handling and adaptation to energetic stress. The limitation is that the human therapeutic evidence is dramatically less developed than for elamipretide.

That leads to a useful conceptual sequence:

Repair/normalize the mitochondrial environment → then stimulate mitochondrial metabolic adaptation.

Or more simply:

SS-31 = RESTORE → MOTS-c = ACTIVATE/ADAPT

The educational protocol addressed in *Peptides for Health*

Rather than starting both on Day 1, I would make the default Millennium mitochondrial sequence:

Weeks 1–4: SS-31 alone
↓
Weeks 5–8: SS-31 continues + introduce MOTS-c
↓
Weeks 9–12: discontinue SS-31; MOTS-c continues
↓
Reassess

I particularly like the 4-week SS-31 lead-in because it accomplishes something clinically useful beyond the theoretical mitochondrial rationale: you can determine the individual's response and tolerability to SS-31 before introducing another experimental agent.

There is precedent for sustained daily SS-31 exposure: mitochondrial-myopathy studies used 40 mg SC daily for 24 weeks, with longer open-label exposure, while other studies have evaluated 20–60 mg/day. This doesn't establish that 4–8 weeks is optimal for your proposed application, but it makes a several-week SS-31 foundation biologically and clinically more defensible than very short cycling.

One important update for the book: SS-31 and MOTS-c should no longer be presented as having equivalent clinical-development status. Elamipretide became an FDA-approved drug in 2025 for the narrow indication of Barth syndrome, whereas MOTS-c remains investigational.

I would therefore characterize the SS-31 → overlap → MOTS-c sequence as the preferred *Peptides for Health/Millennium mitochondrial optimization model*, while explicitly stating that the sequencing itself is mechanistically derived and has not been validated in a controlled combination trial.

Conservative Approach with SS-31 and MOTS-c.

Weeks	SS-31	MOTS-c	Objective
1–4	10 mg SC QD	—	Mitochondrial conditioning / assess tolerance
5–8	10 mg SC QD	5 mg SC 3× weekly	Overlap / metabolic activation
9–12	—	5 mg SC 3× weekly	Metabolic adaptation
After Week 12	Stop	Stop	Reassess before another cycle

SS-31 / Elamipretide —

1. Birk AV, Liu S, Soong Y, et al. The mitochondrial-targeted compound SS-31 re-energizes ischemic mitochondria by interacting with cardiolipin. *J Am Soc Nephrol.* 2013;24(8):1250-1261. PMID: 23813215. PubMed
2. Birk AV, Chao WM, Bracken C, Warren JD, Szeto HH. Targeting mitochondrial cardiolipin and the cytochrome c/cardiolipin complex to promote electron transport and optimize mitochondrial ATP synthesis. *Br J Pharmacol.* 2014;171(8):2017-2028. PMID: 24134698. PubMed
3. Szeto HH. First-in-class cardiolipin-protective compound as a therapeutic agent to restore mitochondrial bioenergetics. *Br J Pharmacol.* 2014;171(8):2029-2050. doi: 10.1111/bph.12461. PMID: 24117165. PubMed
4. Eirin A, Ebrahimi B, Zhang X, et al. Mitochondrial protection restores renal function in swine atherosclerotic renovascular disease. *Cardiovasc Res.* 2014;103(4):461-472. PMID: 24947415. PubMed
5. Daubert MA, Yow E, Dunn G, et al. Novel mitochondria-targeting peptide in heart failure treatment: a randomized, placebo-controlled trial of elamipretide. *Circ Heart Fail.* 2017;10(12):e004389. PMID: 29217757. PubMed
6. Saad A, Herrmann SMS, Eirin A, et al. Phase 2a clinical trial of mitochondrial protection (elamipretide) during stent revascularization in patients with atherosclerotic renal artery stenosis. *Circ Cardiovasc Interv.* 2017;10(9):e005487. PMID: 28916603. PubMed
7. Zhu Y, Wang H, Fang J, et al. SS-31 provides neuroprotection by reversing mitochondrial dysfunction after traumatic brain injury. *Oxid Med Cell Longev.* 2018;2018:4783602. PMID: 30224944. PubMed
8. Campbell MD, Duan J, Samuelson AT, et al. Improving mitochondrial function with SS-31 reverses age-related redox stress and improves exercise tolerance in aged mice. *Free Radic Biol Med.* 2019;134:268-281. PMID: 30597195. PubMed
9. Daubert MA, Yow E, Barnhart HX, et al. Effects of elamipretide on left ventricular function in patients with heart failure with reduced ejection fraction: the PROGRESS-HF Phase 2 trial. *J Card Fail.* 2020;26(5):429-437.. PMID: 32068002. PubMed
10. Karaa A, Haas R, Goldstein A, et al. A randomized crossover trial of elamipretide in adults with primary mitochondrial myopathy. *J Cachexia Sarcopenia Muscle.* 2020;11(4):909-918. PMID: 32096613. PubMed

11. Reid Thompson W, Hornby B, Manuel R, et al. A phase 2/3 randomized clinical trial followed by an open-label extension to evaluate the effectiveness of elamipretide in Barth syndrome, a genetic disorder of mitochondrial cardiolipin metabolism. *Genet Med.* 2021;23(3):471-478. PMID: 33077895. PubMed
12. Silvaroli JA, Bisunke B, Kim JY, et al. Genome-wide CRISPR screen identifies phospholipid scramblase 3 as the biological target of mitoprotective drug SS-31. *J Am Soc Nephrol.* 2024;35(6):681-695. doi: PMID: 38530359. PubMed

MOTS-c

1. Lee C, Zeng J, Drew BG, et al. The mitochondrial-derived peptide MOTS-c promotes metabolic homeostasis and reduces obesity and insulin resistance. *Cell Metab.* 2015;21(3):443-454. PMID: 25738459. PubMed
2. Zarse K, Ristow M. A mitochondrially encoded hormone ameliorates obesity and insulin resistance. *Cell Metab.* 2015;21(3):355-356. PMID: 25738453. PubMed
3. Fuku N, Pareja-Galeano H, Zempo H, et al. The mitochondrial-derived peptide MOTS-c: a player in exceptional longevity? *Aging Cell.* 2015;14(6):921-923. PMID: 26289118. PubMed
4. Lee C, Kim KH, Cohen P. MOTS-c: A novel mitochondrial-derived peptide regulating muscle and fat metabolism. *Free Radic Biol Med.* 2016;100:182-187. PMID: 27216708. PubMed
5. Lu H, Wei M, Zhai Y, et al. MOTS-c peptide regulates adipose homeostasis to prevent ovariectomy-induced metabolic dysfunction. *J Mol Med (Berl).* 2019.
6. Kim SJ, Mehta HH, Wan J, et al. Mitochondrial peptides modulate mitochondrial function during cellular senescence. *Aging (Albany NY).* 2018;10(6):1239-1256. .
7. ***Kim KH, Son JM, Benayoun BA, Lee C. The mitochondrial-encoded peptide MOTS-c translocates to the nucleus to regulate nuclear gene expression in response to metabolic stress. *Cell Metab.* 2018;28(3):516-524.e7.
8. Reynolds JC, Lai RW, Woodhead JST, et al. MOTS-c is an exercise-induced mitochondrial-encoded regulator of age-dependent physical decline and muscle homeostasis. *Nat Commun.* 2021;12:470. PMID: 33473109. PubMed
9. Wan W, Zhang C, Danielsen M, et al. Mitochondria-derived peptide MOTS-c: effects and mechanisms related to stress, metabolism and aging. *J Transl Med.* 2023;21(1):36. PMID: 36670507. PubMed
10. Xiao J, Zhang Q, Shan Y, et al. The mitochondrial-derived peptide (MOTS-c) interacted with Nrf2 to defend the antioxidant system to protect dopaminergic neurons against rotenone exposure. *Mol Neurobiol.* 2023;60(10):5915-5930. PMID: 37380822. PubMed
11. Li F, et al. Neuroprotective mechanism of MOTS-c in TBI mice: insights from integrated transcriptomic and metabolomic analyses. *Drug Des Devel Ther.* 2024. PMID: 39050800. PubMed
12. Shi J, Wu Y, Liu X, et al. MOTS-c, a mitochondrial-derived peptide, ameliorates lysosomal membrane permeability and improves survival of soft tissue transplantation. *Autophagy.* 2026:1-30. PMID: 42153537.
PubMed