

RESEARCH MONOGRAPH · COMPOUND PROFILE

SS-31

A 4-amino-acid mitochondrial-targeting peptide developed at Cornell University, characterized for binding to cardiolipin in the inner mitochondrial membrane and protecting mitochondrial function in oxidative stress.

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ABSTRACT

SS-31 (sequence D-Arg-Dmt-Lys-Phe-NH₂, also known as elamipretide, Bendavia, MTP-131; CAS 736992-21-5; molecular formula C₃₂H₄₉N₉O₅; molecular weight 639.79) is a synthetic tetrapeptide developed in the laboratory of Hazel Szeto at Cornell University Medical College beginning in the early 2000s. The peptide is the most extensively characterized member of the Szeto-Schiller (SS) series of mitochondrial-targeting tetrapeptides. The biological mechanism is binding to cardiolipin in the inner mitochondrial membrane, which protects the membrane lipid environment from peroxidation, stabilizes the supercomplexes of the electron transport chain, and improves mitochondrial efficiency in conditions of oxidative stress or mitochondrial dysfunction. The compound is the active pharmaceutical ingredient in elamipretide (Bendavia), which has been advanced through Phase 2 and Phase 3 clinical trials by Stealth BioTherapeutics for primary mitochondrial myopathies, age-related macular degeneration (dry AMD with geographic atrophy), Barth syndrome, and other mitochondrial dysfunction indications. The clinical record is mixed; the most-promising results have come in Barth syndrome and primary mitochondrial myopathy. The compound is not approved by any regulatory authority for human or veterinary use as of this revision; recent FDA review in geographic atrophy resulted in a complete response letter requesting additional data. The Kodiak biolabs lot of record is SW260307, manufactured 7 March 2026 by Xian Sowu Biotech, with a vendor COA assay of 99.62 percent and a supplementary HPLC area-percent of 99.18 percent at 220 nm; both documents are archived on the lab results page.

Compound identification

Nomenclature and synonyms

The compound is referred to as SS-31, elamipretide, Bendavia, and MTP-131. The "SS" designation refers to the Szeto-Schiller laboratory naming convention (Hazel Szeto and Peter Schiller). The therapeutic development name "elamipretide" was introduced by Stealth BioTherapeutics during clinical development. "Bendavia" is the trade name used during Phase 2 cardiac trials. The CAS number is 736992-21-5.

A related compound is SS-02 (D-Arg-Tyr-Lys-Phe-NH₂), which is the parent SS series compound. SS-31 differs from SS-02 only in the substitution of 2',6'-dimethyltyrosine (Dmt) for tyrosine at position 2; this single modification improves stability and modestly enhances cardiolipin binding affinity. Mass spectrometry distinguishes the two readily.

Structural chemistry

The amino acid sequence is D-arginine - 2',6'-dimethyltyrosine - L-lysine - L-phenylalanine - amide (C-terminal amidation). The presence of D-arginine at the N-terminus and the unnatural Dmt at position 2 confer significant peptidase resistance. The C-terminal amide further extends the half-life relative to a free carboxylate.

The molecular formula is C₃₂H₄₉N₉O₅; the average molecular weight is 639.79 g/mol; the monoisotopic mass is 639.39 daltons. The peptide carries multiple positive charges at physiological pH from the D-arginine guanidinium and the lysine epsilon-amine, balanced partially by the Dmt phenol ionization at higher pH. The net positive charge of approximately +2 is mechanistically important: the cation-rich character of the peptide drives membrane potential-dependent accumulation in mitochondria, where it concentrates by approximately 1000-fold relative to the cytosol.

Physicochemical properties

SS-31 is supplied as a white powder. The lot of record (Kodiak biolabs lot SW260307) conforms to this description. Solubility in water and bacteriostatic water is high; concentrations up to 10 mg/mL are routinely prepared without precipitation. The peptide is also soluble in 0.9 percent saline, PBS, and standard biological buffers. Solubility in DMSO is moderate; DMSO can be used as a co-solvent if necessary but is not the primary vehicle.

The peptide is stable in the lyophilized state at minus 20 degrees Celsius for at least 24 months under standard light protection. Reconstituted solutions in bacteriostatic water are stable at 2 to 8 degrees Celsius for at least 30 days. The Dmt residue contributes mild light sensitivity; protect solutions from prolonged direct sunlight. Freeze-thaw cycles should be avoided.

Discovery and developmental history

Origin in the Szeto-Schiller series

The Szeto-Schiller mitochondrial-targeting peptides emerged from a research program at Cornell University Medical College combining peptide chemistry expertise from Peter Schiller's laboratory with mitochondrial physiology expertise from Hazel Szeto's laboratory. The starting observation was that a series of small cation-rich peptides with alternating aromatic and basic residues (the "SS series") accumulated in mitochondria at concentrations 1000-fold above cytosolic concentrations, driven by the inner mitochondrial membrane potential. The targeting was robust across cell types and across species.

SS-31 was identified in 2004 as the most active member of the series in protecting mitochondrial function against oxidative stress. The cardiolipin-binding mechanism was elucidated over the subsequent decade in collaboration with structural biology groups at Cornell, the National Institutes of Health, and the University of Cologne.

Clinical translation

Stealth BioTherapeutics (now Stealth Biopharmaceuticals) licensed the SS-31 platform from Cornell and has advanced elamipretide through multiple clinical programs. The early Phase 2 work focused on cardiovascular indications (acute coronary syndrome reperfusion injury, heart failure with reduced ejection fraction); the cardiovascular results were mixed. The program subsequently shifted to mitochondrial dysfunction indications, with the strongest results in primary mitochondrial myopathy and Barth syndrome. A Phase 3 trial in dry AMD with geographic atrophy completed in the early 2020s; FDA review resulted in a complete response letter requesting additional data, and the program is in extended discussion with the agency at the time of this revision.

There is no FDA-approved IND for SS-31 in any indication as of this monograph. The compound is not a regulated drug substance in the United States, the European Union, or Japan.

Mechanism of action

Cardiolipin binding

The principal mechanism is binding to cardiolipin, the diphosphatidylglycerol lipid that is enriched in the inner mitochondrial membrane and is essential for the structural and functional integrity of the electron transport chain supercomplexes. The interaction involves both electrostatic contacts between the cation-rich peptide and the dianionic cardiolipin headgroup and hydrophobic contacts between the aromatic Dmt residue and the cardiolipin acyl chains. The binding produces a stabilizing effect on the lipid environment, particularly under conditions where peroxidation or other oxidative damage would otherwise destabilize the supercomplexes.

Protection of supercomplex assembly

The downstream consequence of cardiolipin stabilization is preserved assembly of the respiratory chain supercomplexes (Complex I plus Complex III plus Complex IV in the I-III-IV supercomplex; Complex II is not part of the supercomplex but its associated lipid environment also benefits). Preserved supercomplex assembly correlates with preserved respiratory efficiency, reduced electron leak, and reduced reactive oxygen species production at the inner membrane. The functional consequences are improved ATP production, reduced oxidative damage, and preserved mitochondrial structural integrity.

Reduced reactive oxygen species

SS-31 reduces mitochondrial ROS production both through the supercomplex stabilization (which reduces electron leak at Complexes I and III) and through direct ROS-scavenging by the Dmt residue (which is a mild electron donor in physiological conditions). The combined effect is a substantial reduction in mitochondrial oxidative stress signatures including 4-hydroxynonenal adducts, malondialdehyde, and cardiolipin peroxides.

Indication-specific mechanisms

In primary mitochondrial myopathy and Barth syndrome (the indications with the strongest clinical results), the underlying genetic defect impairs cardiolipin biosynthesis or remodeling. SS-31's cardiolipin-binding activity partially compensates for the genetic deficit by stabilizing the cardiolipin pool that remains. In ischemia-reperfusion injury, SS-31 reduces the burst of ROS and calcium dysregulation that drives reperfusion damage. In age-related macular degeneration, SS-31 protects retinal pigment epithelium mitochondria from chronic oxidative stress.

Limits of the mechanistic model

The cardiolipin-binding mechanism is well established at the biochemical and structural level. The downstream supercomplex stabilization and ROS reduction effects are reproducible across multiple laboratories. The clinical translation has been more complicated; the mixed Phase 2 and Phase 3 results suggest that the magnitude of clinical benefit depends strongly on the specific indication and on baseline mitochondrial dysfunction. Investigators should treat the mechanism as well supported and the clinical case as indication-dependent.

Pharmacokinetics

Routes of administration

Subcutaneous administration is the primary route in clinical trials; intravenous administration has been used in some Phase 2 work. Oral bioavailability is poor due to gastric peptidase degradation and limited intestinal absorption of the cation-rich peptide. The clinical formulation is a stable subcutaneous injectable.

Plasma half-life and tissue distribution

The plasma half-life is approximately 1 to 2 hours following subcutaneous administration. Tissue distribution is mitochondria-focused; the peptide accumulates by approximately 1000-fold in mitochondria relative to cytosol, driven by the inner membrane potential. The biological effect duration extends substantially beyond the plasma half-life because the mitochondrial accumulation persists after plasma clearance. Once-daily dosing maintains effective mitochondrial concentrations in the published clinical protocols.

Metabolism and excretion

SS-31 is hydrolyzed slowly by serum and tissue peptidases due to the D-arginine and Dmt unnatural residues. The peptide is detectable in mitochondrial preparations from treated animals at concentrations sufficient for the proposed cardiolipin-binding mechanism. Major metabolites include the C-terminal dipeptide and shorter fragments; metabolite biological activity has not been extensively characterized. Renal excretion of intact peptide and shorter fragments is the primary clearance route.

Reported research dose ranges

The published preclinical literature reports rodent doses ranging from 0.1 to 10 milligrams per kilogram subcutaneously, with the bulk of pharmacology studies clustering around 1 to 5 milligrams per kilogram daily. Allometric scaling places the equivalent human exposure in the range of 14 to 700 micrograms per kilogram per dose, or approximately 1 to 50 milligrams per dose for a 70 kg subject.

The dose range used in clinical trials of elamipretide is 4 to 60 milligrams per dose subcutaneously, with most trials using 40 milligrams per dose once daily. The dose range commonly cited in research-grade vendor literature (1 to 5 milligrams per research subject, daily, in 4 to 8 week cycles) is at the lower end of the clinical dosing. Investigators should treat the published dose ranges as approximate guidance.

Sourcing and quality verification

Synthesis route

SS-31 is produced by solid-phase peptide synthesis using Fmoc chemistry. The 4-residue length is short, but the synthesis is technically demanding because of the unnatural Dmt residue (which must be incorporated as a Fmoc-protected building block from a specialty supplier) and the C-terminal amidation. Stereochemical preservation of the D-arginine is essential; any racemization to L-arginine substantially reduces the peptidase resistance.

The Kodiak biolabs lot of record is SW260307, manufactured 7 March 2026 by Xian Sowu Biotech (Xian, China; batch size 1200 g; expiry 7 March 2028). The vendor COA records assay value 99.62 percent (greater than the 99.0 percent specification), conformance on appearance, odor, particle size (100 percent through 80-mesh), moisture (under 5 percent), ash content (under 4 percent), solvent residue (Eur.Pharm), total heavy metals (under 10 ppm), arsenic, lead, mercury, DDT, E. coli, GMO status (free), and irradiation (free). The supplementary Shimadzu HPLC report at 220 nm reports the parent peak at 12.205 minutes with area-percent 99.176 percent (rounded to 99.18 percent). Janoshik third-party verification is pending.

Common adulterants and impurities

The research-grade SS-31 supply chain has documented patterns of substandard product. Reported issues include:

1. Substitution of SS-31 with the parent SS-02 compound (which contains tyrosine at position 2 instead of Dmt). The two compounds have different molecular weights (SS-31 at 639.79; SS-02 at approximately 612 Da) and different cardiolipin-binding affinities. Mass spectrometry distinguishes them readily.
2. Racemization of the D-arginine to L-arginine, producing a peptide of correct mass but markedly reduced peptidase resistance and biological half-life. Chiral HPLC is required to detect this.
3. Incomplete C-terminal amidation, producing the free-acid form with reduced cellular uptake. Mass spectrometry detects this (the free acid is approximately 1 dalton heavier).

4. Deletion sequences from incomplete coupling; the tetrapeptide is short enough that deletions produce dipeptide impurities of obviously different mass.
5. Excess acetate or trifluoroacetate counterions inflating apparent mass by 5 to 10 percent.
6. Endotoxin contamination from non-pyrogen-controlled synthesis.

Independent verification by HPLC, mass spectrometry, and chiral HPLC on every batch is essential. The vendor COA is necessary but not sufficient. Kodiak biolabs is in the process of establishing third-party verification through Janoshik Analytical, and the SS-31 entry will be updated when both vendor and Janoshik documentation are received.

Analytical standards

Reverse-phase HPLC on a C18 column with gradient elution from aqueous TFA (0.1 percent) to acetonitrile, monitoring at 215 nm and 280 nm (the latter exploiting the Dmt phenol absorbance), is the standard purity assay. Identity confirmation by LC-MS yields a protonated molecular ion at 640.4 m/z. Chiral HPLC on a Crownpak CR(+) column or similar is required to confirm the D-arginine stereochemistry.

Reconstitution and handling

Solvent system

SS-31 dissolves readily in water, bacteriostatic water, and 0.9 percent saline. The standard reconstitution protocol uses bacteriostatic water for any solution intended for storage beyond a single use. For acute experiments, sterile water for injection or PBS works. DMSO is not the primary vehicle but can be used as a co-solvent at up to 5 percent if necessary.

Reconstitution protocol

A 5 mg vial reconstituted in 1 mL produces a 5 mg/mL solution; in 2 mL produces a 2.5 mg/mL solution. Allow the vial to rest at room temperature for 30 to 60 seconds, then gently swirl until the powder fully dissolves. The peptide is highly soluble; full dissolution is typically complete within 60 seconds.

Storage stability

Lyophilized SS-31 in the unopened vial: stable at minus 20 degrees Celsius for at least 24 months. Reconstituted solutions: stable at 2 to 8 degrees Celsius for at least 30 days. Aliquot working solutions to avoid freeze-thaw cycles and to limit Dmt photochemistry. Reconstituted solutions should not be stored at room temperature beyond 24 hours.

Stack interaction considerations

SS-31 is occasionally combined with NAD⁺ in research-grade protocols on the rationale that both compounds intersect with mitochondrial energetics. The mechanistic case for synergy is plausible (NAD⁺ supports sirtuin activity and mitochondrial biogenesis, both of which complement cardiolipin stabilization) but not formally established in controlled comparison studies.

Combination with other mitochondrial-targeting compounds (MitoQ, idebenone, Coenzyme Q10) has been studied in some preclinical models. The combination with MitoQ in particular is mechanistically interesting because MitoQ is a mitochondrial-targeting antioxidant with a distinct mechanism (CoQ10 mimic accumulating in mitochondria via a triphenylphosphonium cation) and the two approaches may be additive.

Pharmacokinetic interactions with CYP-substrate compounds are not expected. SS-31 has no documented receptor-level interactions with conventional small-molecule pharmacotherapy.

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