BIOMOD LABS · RESEARCH PEPTIDE CO.

RESEARCH COMPOUND MONOGRAPH · SERIES 1 · NO. 017

SS-31 / Elamipretide

D-Arg-Dmt-Lys-Phe-NH_2 — a Szeto-Schiller mitochondria-targeting tetrapeptide that binds cardiolipin in the inner mitochondrial membrane, modulates cristae morphology, and restores electron transport chain function in preclinical mitochondrial-dysfunction models.

CAS REGISTRY	CATALOG REFERENCE	CLASS	DATE OF ISSUE
736992-21-5	BM-LYO-017	Synthetic tetrapeptide · 4 a.a.	May 2026

SS-31 (development codes MTP-131, Bendavia, Elamipretide) is a synthetic amphipathic tetrapeptide of sequence D-Arg-Dmt-Lys-Phe-NH_2 (where Dmt is 2,6-dimethyltyrosine) developed by Hazel Szeto and Peter Schiller as part of the Szeto-Schiller "SS" peptide family. The Szeto-Schiller peptides were discovered serendipitously during structure-activity work on opioid receptor ligands at Weill Cornell Medical College, when the alternating cationic-aromatic motif characteristic of these tetrapeptides was found to confer mitochondrial selectivity rather than predominant opioid pharmacology. SS-31 binds cardiolipin, the anionic phospholipid uniquely localised to the inner mitochondrial membrane, and modulates inner-membrane cristae morphology, stabilises electron transport chain supercomplexes, supports cytochrome c electron-carrying function while reducing its peroxidase activity, and inhibits opening of the mitochondrial permeability transition pore in mitochondrial-stress preparations. ***This monograph summarises published cellular pharmacology and preclinical findings for laboratory research reference only.***

01 Compound Profile

COMMON DESIGNATION	SS-31 · Elamipretide · MTP-131 · Bendavia
PRIMARY SEQUENCE	D-Arg-Dmt-Lys-Phe-NH_2 (where Dmt = 2,6-dimethyl-L-tyrosine)
MODIFICATIONS	D-Arg at position 1 (protease resistance); 2,6-dimethyltyrosine at position 2 (radical-scavenging redox-active phenol); C-terminal amide
CAS REGISTRY	736992-21-5
MOLECULAR FORMULA	$C_{32}H_{49}N_9O_5$
AVERAGE MOLECULAR MASS	639.79 g · mol^{-1}
PRIMARY MOLECULAR TARGET	Cardiolipin in the inner mitochondrial membrane — the anionic phospholipid that is enriched in mitochondrial inner membranes and is essential for electron transport chain supercomplex organisation[1]
MITOCHONDRIAL ACCUMULATION	Approximately 1000-fold accumulation in mitochondria relative to extracellular concentration; cell-permeable through standard plasma membranes
PHYSICAL FORM	White lyophilised solid
SOLUBILITY (LAB RECONSTITUTION)	Highly water-soluble; the alternating cationic-aromatic motif confers excellent aqueous solubility
STORAGE (RESEARCH HANDLING)	Lyophilised solid: −18 °C, desiccated, light-protected (Dmt2 and Phe4 are aromatic, photo-oxidation considerations apply); reconstituted solution refrigerated 2–8 °C short-term; aliquoted long-term at −18 °C
ANALYTICAL SPECIFICATION	≥ 98 % purity by HPLC (BIOMOD Labs internal release specification)

02 Origin and Chemistry

The Szeto-Schiller peptide family was discovered at Weill Cornell Medical College during structure-activity work on opioid receptor ligands. Szeto and Schiller observed that synthetic tetrapeptides with alternating cationic (D-Arg, Lys) and aromatic (Dmt, Phe) side chains exhibited unusual cellular distribution patterns — accumulating in mitochondria to approximately 1000-fold extracellular concentration despite the absence of any

classical mitochondrial targeting sequence. The cationic-aromatic-cationic-aromatic motif of SS-31 confers a unique combination of cell-permeability (alternating hydrophobicity) and mitochondrial-membrane affinity (positive charge attracted to the highly anionic cardiolipin-rich inner mitochondrial membrane).[1, 2]

The 2,6-dimethyltyrosine (Dmt) at position 2 contributes a redox-active phenol that was initially proposed to function as a mitochondrial-targeted antioxidant — quenching reactive oxygen species through tyrosyl radical formation and subsequent radical-radical coupling to ditryrosine. Subsequent work has refined this picture: cardiolipin binding and inner-membrane cristae modulation are now understood as the principal mechanism, with the antioxidant chemistry being a contributing but not dominant effect.[3, 4]

03 Molecular Targets and Cellular Signalling

SS-31's principal mitochondrial target is cardiolipin (CL), the unique tetraacyl-phosphatidylglycerol lipid that constitutes approximately 20% of inner mitochondrial membrane phospholipids and is essential for electron transport chain supercomplex organisation. The Birk and Szeto 2014 work characterised the molecular interaction: SS-31 binds cardiolipin via the alternating cationic-aromatic motif, modulating the hydrophobic interaction between cytochrome c and cardiolipin in a manner that promotes electron-carrying function while reducing the peroxidase activity of the cytochrome c–cardiolipin complex (which contributes to oxidative damage under stress). The 2020 mass-spectrometry cross-linking study by Chavez and colleagues identified mitochondrial protein interactors of SS-31, all known cardiolipin-binding proteins, falling into two groups: oxidative phosphorylation pathway components and 2-oxoglutarate metabolic enzymes.[4]

Additional preclinical mechanisms include: **cristae morphology preservation** — SS-31 prevents inner-membrane cristae fragmentation in mitochondrial-stress preparations; **respiratory complex stabilisation** — supercomplexes I-III-IV organisation maintained; **permeability transition pore inhibition** — opening of the mPTP under mitochondrial-stress conditions is reduced; **antioxidant activity** — Dmt2 radical-scavenging chemistry contributes to ROS attenuation; **mitochondrial-restricted action** — SS-31 has no effect on healthy, unstressed mitochondria.[3, 5] PRECLINICAL · MOUSE

04 Preclinical Findings

SYSTEM	ANIMAL MODEL / PREPARATION	REPORTED OBSERVATION	REF.
Cardiolipin binding	Cell-free lipid bilayer biophysics	Defined cardiolipin-binding chemistry; ~1000-fold mitochondrial accumulation	2
Mitochondrial protein interactors	Cross-linking mass spectrometry	Cardiolipin-binding OXPHOS proteins and 2-oxoglutarate metabolism proteins identified	4
Cardiac mitochondrial function	Aged mouse cardiac preparations	Restoration of mitochondrial function and cardiac performance in aged animals	6
Skeletal muscle bioenergetics	Single SS-31 injection to old mice	Enhanced mitochondrial energetics in skeletal muscle	5
Renal mitochondrial preservation	Rodent acute kidney injury models	Preservation of mitochondrial structure and function; reduced ROS in proteinuria preparations	3

SYSTEM	ANIMAL MODEL / PREPARATION	REPORTED OBSERVATION	REF.
Cardiolipin-protective compound	Multiple mitochondrial-stress preparations	First-in-class cardiolipin-protective compound	1

05 Research Synthesis & Limitations

METHODOLOGICAL NOTES

SS-31 is one of the most thoroughly characterised mitochondrial-targeted research peptides, with foundational chemistry from the Szeto-Schiller laboratory and substantial follow-on biophysics, structural biology, and animal-pharmacology characterisation by multiple independent groups. The mechanistic understanding has shifted over approximately two decades — from "mitochondrial-targeted antioxidant" to "cardiolipin-binding mitochondrial-membrane stabiliser" — and researchers should design experiments with the current mechanistic understanding in mind. The Dmt2 residue is non-standard and reduces commercial availability of the compound compared to all-natural-amino-acid peptides. The molecule's restricted action on stressed (but not healthy) mitochondria is a notable pharmacological feature.

06 Laboratory Handling, Reconstitution, and Storage

Lyophilised SS-31 is supplied under research-use specifications. The alternating cationic-aromatic motif confers excellent water solubility. Reconstitution in sterile water for injection, phosphate-buffered saline, or bacteriostatic water is standard practice. The aromatic residues (Dmt2 and Phe4) are mildly photo-oxidation susceptible; light protection is recommended. Lyophilised storage at −18 °C, desiccated, light-protected; reconstituted solutions held refrigerated 2–8 °C for short-term work; aliquoted long-term storage at −18 °C with minimised freeze–thaw. Working concentrations are determined by the investigator's experimental design.

07 References

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