

RESEARCH MONOGRAPH . COMPOUND PROFILE

FOXO4-DRI Peptide

A retroinverso D-amino acid peptide that disrupts the FOXO4-p53 interaction in senescent cells, selectively triggering apoptosis.

DOCUMENT	KDC-MN-300
ISSUED	2026-05-09
REVISION	1.0
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COMPOUND CLASS	Cell-penetrating peptide senolytic

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ABSTRACT

FOXO4-DRI (FOXO4-D-retroinverso peptide; sequence ltlrkepaseiaqsileayqqgs in D-amino acids; molecular weight approximately 2700 Da) is a designed cell-penetrating peptide senolytic developed by de Keizer and colleagues at the Hubrecht Institute. The compound is a retroinverso peptide derived from the FOXO4 sequence that competitively disrupts the FOXO4-p53 interaction; in senescent cells, FOXO4 sequesters nuclear p53 and prevents apoptosis. The DRI peptide releases p53, which translocates to mitochondria and triggers selective apoptosis in senescent cells while sparing healthy cells (which do not depend on the FOXO4-p53 interaction for survival). Mouse studies (Cell 2017) demonstrated dramatic rejuvenation of fur density, kidney function, and physical performance in aged mice. The retroinverso D-amino acid construction confers protease resistance; cell penetration is supported by an attached penetratin sequence. No human clinical trials at this writing. The compound is a research tool for academic senolytic biology.

1. Compound Identification

FOXO4-DRI Peptide is described as cell-penetrating peptide senolytic. A retroinverso D-amino acid peptide that disrupts the FOXO4-p53 interaction in senescent cells, selectively triggering apoptosis.

1.1 Class summary

Cell-penetrating peptide senolytic

1.2 Subtitle

A retroinverso D-amino acid peptide that disrupts the FOXO4-p53 interaction in senescent cells, selectively triggering apoptosis.

2. Abstract

FOXO4-DRI (FOXO4-D-retroinverso peptide; sequence ltlrkepaseiaqsileayqqgs in D-amino acids; molecular weight approximately 2700 Da) is a designed cell-penetrating peptide senolytic developed by de Keizer and colleagues at the Hubrecht Institute. The compound is a retroinverso peptide derived from the FOXO4 sequence that competitively disrupts the FOXO4-p53 interaction; in senescent cells, FOXO4 sequesters nuclear p53 and prevents apoptosis. The DRI peptide releases p53, which translocates to mitochondria and triggers selective apoptosis in senescent cells while sparing healthy cells (which do not depend on the FOXO4-p53 interaction for survival). Mouse studies (Cell 2017) demonstrated dramatic rejuvenation of fur density, kidney function, and physical performance in aged mice. The retroinverso D-amino acid construction confers protease resistance; cell penetration is supported by an attached penetratin sequence. No human clinical trials at this writing. The compound is a research tool for academic senolytic biology.

3. Mechanism of Action

Retroinverso D-amino acid peptide that disrupts FOXO4-p53 interaction; releases p53 to trigger selective apoptosis in senescent cells.

The mechanistic profile described above represents the consensus position from peer-reviewed literature where available; for compounds with sparse formal characterization, this section reflects vendor-grade reports and structurally-related class pharmacology and should be interpreted with appropriate caution.

4. Pharmacokinetics and Routes of Administration

Pharmacokinetic data are summarized within the abstract for compounds with formal Phase 1 records. Compounds without published human pharmacokinetic studies are noted as such; investigators should treat the absence of data as a research limitation.

5. Reported Research Dose Ranges

Mouse studies 5 mg/kg intraperitoneal three times per week.

Doses are scaled from clinical use where the compound is approved as a medicine, from Phase 2/3 trials where development advanced, or from rodent dose-response data scaled by allometric assumptions where the compound has no human clinical record. Investigators should treat dose ranges from research-chemical-grade vendors as starting points for their own pharmacokinetic and tolerability characterization rather than validated dosing recommendations.

6. Sourcing and Quality Verification

Investigators should obtain analytical confirmation of identity (mass spectrometry; for peptides, additionally amino acid analysis or N-terminal sequencing) and purity (HPLC area-percent, ideally greater than 95 percent) on every lot. Vendor certificates of analysis vary in quality; third-party analytical confirmation through independent laboratories (e.g., Janoshik Analytical, Anabolic Lab) is the gold standard for research-grade peptides and small molecules.

For compounds with established pharmaceutical-grade marketing in any jurisdiction, sourcing from the marketed product (where legal and accessible) provides the highest quality assurance.

7. Reconstitution and Handling

Peptides should be reconstituted in bacteriostatic water or sterile water for injection in the volume appropriate to the desired concentration; lyophilized peptides should be allowed to come to room temperature before reconstitution to minimize precipitation. Reconstituted peptides should be stored refrigerated and used within the timeframe specified by the manufacturer (typically 14 to 30 days for bacteriostatic water reconstitutions, shorter for sterile water).

Small molecules: storage conditions vary by compound; consult the certificate of analysis for the specific product. Most are stable at room temperature in dry, dark conditions; oxidation-sensitive compounds (e.g., catecholamine precursors) require cool storage and protection from light.

8. Stack Interaction Considerations

Investigators combining this compound with other research substances should consider receptor-level interactions (additive effects at shared targets), enzyme-level interactions (CYP-mediated drug-drug interactions where applicable), and pharmacodynamic interactions (additive sedation, additive serotonergic activity, additive hemodynamic effects).

The stack interaction section in published monographs of well-characterized compounds is necessarily incomplete for any specific combination; investigators should treat novel combinations with elevated caution and titrate gradually.

9. References

1. Baar MP, et al. Targeted apoptosis of senescent cells restores tissue homeostasis in response to chemotoxicity and aging. Cell 2017.
2. de Keizer PLJ. The fountain of youth by targeting senescent cells? Trends Mol Med 2017.
3. van der Horst A, Burgering BMT. Stressing the role of FoxO proteins in lifespan and disease. Nat Rev Mol Cell Biol 2007.

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