

RESEARCH MONOGRAPH . COMPOUND PROFILE

GDF-11

A growth differentiation factor in the TGF-beta superfamily originally implicated in parabiosis-mediated rejuvenation and subsequently a focus of contested replication studies in cardiac and skeletal muscle aging.

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AUTHOR	Kodiac biolabs Research
COMPOUND CLASS	TGF-beta superfamily growth differentiation factor

ABSTRACT

GDF-11 (growth differentiation factor 11; bone morphogenetic protein 11, BMP-11; CAS 268544-12-9; mature peptide molecular weight approximately 12.5 kDa as a homodimer) is a member of the transforming growth factor beta (TGF-beta) superfamily, closely related to myostatin (GDF-8) with which it shares approximately 90 percent amino acid identity in the mature C-terminal domain. The compound came to prominence in 2013 when a heterochronic parabiosis study by Amy Wagers and Richard Lee at the Harvard Stem Cell Institute identified GDF-11 as a putative young-blood-borne rejuvenation factor that reversed age-related cardiac hypertrophy when administered to old mice. Subsequent studies extended the proposed rejuvenation activity to skeletal muscle and the central nervous system. The original GDF-11 papers triggered substantial follow-up research and substantial contested replication: independent groups (notably the Glass laboratory at Eli Lilly and the Wagers laboratory's own subsequent work) reported that the original immunoassays did not adequately distinguish GDF-11 from myostatin, that circulating GDF-11 levels do not in fact decline with age, and that recombinant GDF-11 administered to old mice produces muscle wasting at high doses (consistent with the myostatin-like activity expected from the structural homology) rather than rejuvenation. The contested literature has not produced consensus; some groups continue to report modest pro-cardiac and pro-cognitive effects of GDF-11 at carefully titrated doses, while others find no effect or harmful effects. Mechanism is canonical TGF-beta superfamily signaling through ActRIIA/B receptors and downstream SMAD2/3 transcription factor activation; GDF-11 and myostatin share the

same receptor and signaling pathway, distinguishing them principally through tissue-specific expression patterns and post-translational propeptide regulation. The compound is research-grade with no regulatory approval and no active clinical development. Investigators studying GDF-11 should be aware of the contested replication literature and the importance of distinguishing GDF-11 from myostatin in immunoassays.

1. Compound Identification

GDF-11 is described as tgfbeta superfamily growth differentiation factor. A growth differentiation factor in the TGF-beta superfamily originally implicated in parabiosis-mediated rejuvenation and subsequently a focus of contested replication studies in cardiac and skeletal muscle aging.

1.1 Class summary

TGF-beta superfamily growth differentiation factor

1.2 Subtitle

A growth differentiation factor in the TGF-beta superfamily originally implicated in parabiosis-mediated rejuvenation and subsequently a focus of contested replication studies in cardiac and skeletal muscle aging.

2. Abstract

GDF-11 (growth differentiation factor 11; bone morphogenetic protein 11, BMP-11; CAS 268544-12-9; mature peptide molecular weight approximately 12.5 kDa as a homodimer) is a member of the transforming growth factor beta (TGF-beta) superfamily, closely related to myostatin (GDF-8) with which it shares approximately 90 percent amino acid identity in the mature C-terminal domain. The compound came to prominence in 2013 when a heterochronic parabiosis study by Amy Wagers and Richard Lee at the Harvard Stem Cell Institute identified GDF-11 as a putative young-blood-borne rejuvenation factor that reversed age-related cardiac hypertrophy when administered to old mice. Subsequent studies extended the proposed rejuvenation activity to skeletal muscle and the central nervous system. The original GDF-11 papers triggered substantial follow-up research and substantial contested replication: independent groups (notably the Glass laboratory at Eli Lilly and the Wagers laboratory's own subsequent work) reported that the original immunoassays did not adequately distinguish GDF-11 from myostatin, that circulating GDF-11 levels do not in fact decline with age, and that recombinant GDF-11 administered to old mice produces muscle wasting at high doses (consistent with the myostatin-like activity expected from the structural homology) rather than rejuvenation. The contested literature has not produced consensus; some groups continue to report modest pro-cardiac and pro-cognitive effects of GDF-11 at carefully titrated doses, while others find no effect or harmful effects. Mechanism is canonical TGF-beta superfamily signaling through ActRIIA/B receptors and downstream SMAD2/3 transcription factor activation; GDF-11 and myostatin share the same receptor and signaling pathway, distinguishing them principally through tissue-specific expression patterns and post-translational propeptide regulation. The compound is research-grade with no regulatory approval and no active clinical development. Investigators studying GDF-11 should be aware of the contested replication literature and the importance of distinguishing GDF-11 from myostatin in immunoassays.

3. Mechanism of Action

TGF-beta superfamily signaling through ActRIIA and ActRIIB receptors with downstream SMAD2/3 activation. Same receptor pathway as myostatin (GDF-8); high amino acid identity in the mature C-terminal domain.

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

Rodent research-grade dosing 0.1 to 1 mg/kg intraperitoneal daily, with the strong caveat that effects above 0.3 mg/kg trend toward myostatin-like muscle wasting in published independent replications.

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. Loffredo FS, et al. Growth differentiation factor 11 is a circulating factor that reverses age-related cardiac hypertrophy. *Cell* 2013.
2. Eggerman MA, et al. GDF11 increases with age and inhibits skeletal muscle regeneration. *Cell Metab* 2015.
3. Smith SC, et al. GDF11 does not rescue aging-related pathological hypertrophy. *Circ Res* 2015.
4. Hammers DW, et al. Supraphysiological levels of GDF11 induce striated muscle atrophy. *EMBO Mol Med* 2017.

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