BPC-157 — C-TERMINAL FRAGMENT TRUNCATION: RETAIN ONLY RESIDUES 10-15 (DDAGLV), REMOVING THE N-TERMINAL GEPPPGKPA SEGMENT TO ISOLATE THE PUTATIVE VEGFR2-INTERACTING ACIDIC/HYDROPHOBIC MOTIF

generated 2026-05-03T10:56:14.596503+00:00

PROMISING REGENERATIVE
C-TERMINAL FRAGMENT TRUNCATION: RETAIN ONLY RESIDUES 10-15 (DDAGLV), REMOVING THE N-TERMINAL GEPPPGKPA SEGMENT TO ISOLATE THE PUTATIVE VEGFR2-INTERACTING ACIDIC/HYDROPHOBIC MOTIF
VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR 2

AVERAGE CONFIDENCE	PTM / IPTM	VERDICT
63.5%	0.361 / 0.649	PROMISING
TARGET	**UNIPROT**	**BINDING PROBABILITY**
Vascular endothelial growth factor receptor 2	P35968	—

TLDR

FOLD №32 isolates the C-terminal hexapeptide DDAGLV from the 15-residue BPC-157 sequence to test whether this fragment alone constitutes a minimal VEGFR2-binding pharmacophore. The structural prediction yields a moderate pLDDT of 0.64 with a notably stronger ipTM of 0.65, suggesting the docked pose has internal consistency even if backbone confidence is only middling. The tandem aspartate orientation toward the receptor surface is promising, but a competing literature hypothesis assigns the active pharmacophore to the N-terminal proline-

rich segment rather than this C-terminal fragment. The signal is interesting enough to pursue further but too ambiguous for a high-confidence verdict.

EXECUTIVE SUMMARY

FOLD №32 predicts that BPC-157's C-terminal hexapeptide DDAGLV adopts an extended docking pose at VEGFR2 (ipTM 0.649), consistent with a minimal acidic pharmacophore hypothesis — but a competing preprint assigns activity to the N-terminal segment we removed, leaving the pharmacophore question genuinely open.

DETAILED ANALYSIS

BPC-157 (GEPPPGKPADDAGLV) is a synthetic 15-amino acid pentadecapeptide originally derived from human gastric juice that has attracted substantial preclinical interest for its tissue regenerative and pro-angiogenic properties. The mechanistic consensus, anchored primarily by Hsieh et al. (2017), positions VEGFR2 activation and downstream Akt-eNOS signaling as central to its biology. What remains entirely unresolved — and forms the intellectual basis of this fold — is which segment of the sequence is responsible for receptor engagement. No binding affinity measurements, no co-crystal structure, and no published truncation or alanine-scanning study exists for BPC-157 at any defined receptor target. FOLD №32 is, to our knowledge, the first computational truncation study specifically designed to interrogate this question.

The modification strategy is a fragment/truncation: residues 1–9 (GEPPPGKPA) are removed entirely, leaving only the six C-terminal residues DDAGLV. The hypothesis is that the tandem aspartates (D10–D11 in full-length numbering) mimic acidic VEGF-A loop residues that contact the VEGFR2 Ig-domain interface, and that the proline-rich N-terminal stretch is merely a conformationally flexible scaffold rather than a contact element. This is a direct and testable pharmacophore hypothesis, and the fragment-first approach is the most parsimonious way to probe it computationally before committing resources to synthesis.

The structural prediction supports a moderate level of optimism. The hexapeptide adopts an extended conformation consistent with the hypothesized β-strand-like receptor-docking geometry rather than a collapsed random coil — a meaningful positive signal given that short isolated fragments frequently lose ordered structure. The ipTM of 0.649 is the most interpretively important metric here: it reflects the internal consistency of the protein–peptide docked pose, and at this length a value near 0.65 indicates the interface geometry is not random. The backbone pLDDT of 0.636 is moderate, which is expected and appropriate for a hexapeptide; very high pLDDT values for sub-ten-residue peptides would themselves be suspicious. The

pTM of 0.361 is lower, reflecting the challenge of confidently placing a tiny fragment in the overall structural ensemble, and should not be over-interpreted negatively.

The biological significance of the tandem aspartate motif is genuinely interesting. VEGF-A engages VEGFR2 through its β-hairpin loops, with acidic residue patches playing key contact roles at the Ig-domain interface. That BPC-157's only acidic residues are both concentrated in the C-terminal DDAGLV segment — rather than distributed across the full sequence — is structurally notable. The hydrophobic GLV tail could plausibly contribute to a shallow hydrophobic groove interaction of the type seen in short peptide–receptor docking. The predicted extended conformation, with aspartates oriented toward the receptor surface in the docked pose, is at least geometrically consistent with this hypothesis.

However, the competing pharmacophore hypothesis must be taken seriously. The Schlosser preprint (2025, unreviewed) argues that the GEPPPGKPA segment adopts a polyproline II helix that engages SH3 domains of Src family kinases — a mechanistically coherent model given that PxxP motifs are canonical SH3 ligands. If this model is correct, the DDAGLV fragment is not a pharmacophore but a C-terminal appendage, and our truncation would produce a biologically inert fragment. The experimental data from Hsieh et al. does not resolve this: VEGFR2 activation could be downstream of SFK-mediated transactivation rather than direct extracellular ligand engagement. This ambiguity is the central limitation of the fold.

Heuristic physicochemical properties add nuance. The stability score of 0.5 (moderate) and short predicted half-life (~15–45 minutes) indicate that DDAGLV, as a free hexapeptide, is likely susceptible to rapid proteolytic degradation in vivo — a concern compounded by the absence of the N-terminal proline-rich segment, which in the full-length peptide may provide some protease resistance through its polyproline geometry. The aggregation propensity of 0.0 is favorable and the BBB penetration estimate of 0.503 is marginally positive, though both are heuristic estimates with limited reliability for a fragment of this size. These properties do not disqualify the fragment but underscore that if DDAGLV shows any activity, metabolic stabilization would be the immediate next modification priority.

This fold connects thematically to the broader regenerative peptide work in this lab. The REFINED TB-500 fold (#28) demonstrated that even a seven-residue fragment can achieve strong structural confidence (pLDDT 0.81) when a macrocyclic constraint pre-organizes the conformation. The contrast is instructive: DDAGLV achieves moderate but meaningful docking confidence without any backbone constraint, which raises the question of whether a similar lactam bridge or staple — analogous to what worked in fold #28 — might pre-organize the DDAGLV fragment and boost both structural confidence and receptor affinity. That would be a logical follow-on fold if this signal strengthens.

RESEARCH BRIEF

FOLD №32 — BPC-157 C-TERMINAL FRAGMENT DDAGLV FOR VEGFR2 ENGAGEMENT

Verdict: PROMISING | Peptide class: Regenerative | Target: VEGFR2 (KDR, P35968)

MECHANISM OF ACTION

BPC-157 (GEPPPGKPADDAGLV) is a 15-residue synthetic peptide derived from human gastric juice with broad preclinical tissue regenerative activity. Its best-characterized pro-angiogenic mechanism runs through VEGFR2: Hsieh et al. (2017, PMID:27847966) demonstrated that BPC-157 increases VEGFR2 mRNA and protein expression in human vascular endothelial cells, promotes dynamin-dependent receptor internalization, and activates the VEGFR2–Akt–eNOS signaling axis — without upregulating VEGF-A itself. This pattern is consistent with a ligand-mimicry model in which BPC-157 engages VEGFR2 directly, bypassing the endogenous growth factor. Downstream, VEGFR2–Akt–eNOS signaling promotes endothelial proliferation, migration, and nitric oxide-mediated vasodilation — mechanisms central to angiogenesis and tissue repair.

A competing mechanistic model (Schlosser preprint, 2025, unreviewed) proposes that the N-terminal GEPPPGKPA segment adopts a polyproline II helix engaging SH3 domains of Src family kinases, with VEGFR2 activation occurring downstream via receptor transactivation rather than direct extracellular ligand engagement. This model is computationally derived and unvalidated by functional assays, but it is mechanistically coherent and must be held as a live alternative hypothesis.

MODIFICATION RATIONALE

FOLD №32 tests whether the C-terminal hexapeptide **DDAGLV** (residues 10–15 of BPC-157) constitutes a minimal pharmacophore sufficient for VEGFR2 engagement. The rationale has three elements:

1. **Acidic residue pharmacophore hypothesis**: The tandem aspartates D10–D11 are the only acidic residues in the full 15-amino acid sequence and are concentrated entirely in the C-terminal DDAGLV fragment. VEGF-A contacts VEGFR2 primarily through β-hairpin loops bearing acidic patches; D10–D11 may mimic this chemistry at the Ig-domain interface.

2. **N-terminal scaffold hypothesis**: The proline-rich GEPPPGKPA segment (residues 1–9) is conformationally flexible and may function as a non-pharmacophoric spacer rather than a receptor-contact element. Removing it should, on this hypothesis, expose the active motif rather than destroy it.
3. **Fragment efficiency logic**: Isolating a minimal pharmacophore reduces molecular weight, potentially improves target selectivity, and creates a scaffold for subsequent optimization (cyclization, stapling, non-natural amino acid incorporation).

This approach diverges from folds #29–31 (Aib substitutions and a stapled peptide on other peptides) by introducing a fragment/truncation strategy with an affinity focus — the first such modification in this lab's BPC-157 series.

PREDICTED PROPERTIES (WHERE SIGNAL IS MODERATE)

Metric	Value	Interpretation
pLDDT	0.635	Moderate backbone confidence; appropriate for hexapeptide length
pTM	0.361	Low global fold confidence; expected given fragment size
ipTM	**0.649**	**Strongest signal; indicates internally consistent docked pose**
Predicted conformation	Extended / β-strand-like	Consistent with receptor-docking hypothesis; not collapsed coil
Aggregation propensity	0.0	Favorable
Stability score	0.5	Moderate; degradation risk is real
Predicted half-life	~15–45 min	Short; unprotected free hexapeptide
BBB penetration (heuristic)	0.503	Marginally positive; low confidence for fragment this size

The ipTM of 0.649 is the primary positive signal in this run. For a six-residue fragment docked to a large receptor, an ipTM approaching 0.65 indicates the interface geometry is non-random and has internal consistency across the prediction. The extended backbone conformation — with tandem aspartates appearing oriented toward the receptor surface and the GLV face forming a compact hydrophobic patch — is geometrically consistent with the ligand-mimicry

hypothesis. This is not a confident binding prediction; it is a structurally plausible docked pose that warrants follow-up.

WHAT WOULD STRENGTHEN THIS SIGNAL

Computational next steps:

1. **Ensemble prediction**: Run DDAGLV vs. VEGFR2 across multiple seeds and sampling temperatures in AlphaFold3/Chai-1 to assess whether the extended conformation and ipTM ~0.65 are reproducible or run-specific. Single-run predictions at this confidence level cannot be interpreted without ensemble context.
2. **Counter-fragment fold**: Predict the complementary N-terminal fragment GEPPPGKPA vs. VEGFR2 under identical conditions. If ipTM for the N-terminal fragment exceeds that of DDAGLV, the Schlosser SH3 model gains computational support and this truncation hypothesis is challenged. If GEPPPGKPA shows lower ipTM against VEGFR2 (but perhaps higher against a Src-SH3 domain), the pharmacophore assignment becomes cleaner.
3. **Constrained DDAGLV variants**: A lactam-bridged or stapled DDAGLV — analogous to the i,i+3 lactam bridge used in TB-500 fold #28 (REFINED, pLDDT 0.81) — could pre-organize the extended conformation and potentially improve both pLDDT and ipTM. Fold #28 demonstrated clearly that macrocyclic constraints on short regenerative peptides can substantially boost structural confidence.
4. **Alanine scan predictions**: Predict D1A-DAGLV and DD-A-GLV variants to assess whether each aspartate independently contributes to the docked pose geometry — a computational surrogate for classical alanine scanning.

Experimental validation (wet lab):

1. **Direct binding assay**: Surface plasmon resonance (SPR) or fluorescence polarization with synthesized DDAGLV and the VEGFR2 extracellular domain (Ig-domains 1–3) would definitively test whether this fragment binds. Given the complete absence of any published BPC-157 binding affinity data, even a negative result here would be a significant contribution to the field.
2. **Cellular activity assay**: HUVEC tube formation and VEGFR2 phosphorylation (pY1175) assays comparing DDAGLV, full-length BPC-157, and the N-terminal GEPPPGKPA fragment would functionally map which segment drives downstream signaling.
3. **Protease stability profiling**: Given the predicted short half-life (~15–45 min), a plasma stability assay on synthetic DDAGLV should precede any cell-

based work to determine whether the fragment survives long enough to be biologically interpretable.

CROSS-FOLD CONNECTIONS

This fold sits within the lab's broader regenerative peptide programme alongside the TB-500 series (folds #7, #16, #28). The contrast with **fold #28** (TB-500 lactam bridge, REFINED, pLDDT 0.81) is instructive: that work demonstrated that macrocyclic pre-organization of a short regenerative heptapeptide can push structural confidence into the high-reliability range. DDAGLV achieves moderate docking confidence without any backbone constraint — which is either a genuine positive signal or an artefact of a permissive run. A constrained DDAGLV variant would test this directly and represents the most logical immediate next fold in this series.

Fold #16 (TB-500 Lys→Orn, DISCARDED) serves as a useful cautionary comparison: a single conservative substitution that seemed unlikely to disturb function nonetheless produced a biologically uninformative prediction. Fragment truncation is a far more aggressive modification than single-residue substitution, and the possibility that DDAGLV is simply a biologically inert fragment of a larger active scaffold cannot be excluded on the current data.

SEQUENCES

NATIVE

```
GEPPPGKPADDAGLV
```

MODIFIED

```
DDAGLV
```

CAVEATS

- in silico prediction only — requires wet lab validation
- single-run prediction (not ensembled); ipTM 0.65 on a hexapeptide needs ensemble confirmation across multiple seeds
- predicted properties may not reflect real-world biological behavior
- this is research, not medical advice
- fragment truncation removes the N-terminal proline-rich segment that an unreviewed preprint (Schlosser 2025) proposes as the primary pharmacophore —

if that model is correct, DDAGLV is biologically inert and this prediction is misleading

- no published binding affinity (Kd, IC50) or structural data exists for BPC-157 at VEGFR2; all mechanistic inferences are from cellular signaling readouts, not direct binding measurements
- heuristic physicochemical values (half-life, BBB, stability, aggregation) are sequence-based estimates only — not experimental measurements; short hexapeptide fragments are particularly unreliable inputs for these heuristics
- predicted short half-life (~15–45 min) suggests DDAGLV would require metabolic stabilization for any meaningful in vivo or cellular activity testing
- pTM of 0.361 reflects low global structural confidence; only the ipTM metric is interpretively useful for this fragment-receptor prediction

CITATIONS

1. **PMID —** (2017) — — Therapeutic potential of pro-angiogenic BPC157 is associated with VEGFR2 activation and up-regulation.
2. **PMID —** (2025) — — BPC-157 Binding to SH3 Domains and Activation of Src Family Kinases: In Silico Modeling and Fluorescent Fusion Protein Production
3. **PMID —** (2025) — — BPC-157 Predicted to Bind SH3 Domains and Activate Src Family Kinases: In Silico Modeling and Fluorescent Fusion Protein Validation
4. **PMID —** (2025) — — Regeneration or Risk? A Narrative Review of BPC-157 for Musculoskeletal Healing.
5. **PMID —** (2018) — — BPC 157 and Standard Angiogenic Growth Factors. Gastrointestinal Tract Healing, Lessons from Tendon, Ligament, Muscle and Bone Healing.
6. **PMID —** (2021) — — Stable Gastric Pentadecapeptide BPC 157 and Wound Healing.
7. **PMID —** (2025) — — Multifunctionality and Possible Medical Application of the BPC 157 Peptide-Literature and Patent Review.
8. **PMID —** (2019) — — Gastric pentadecapeptide body protection compound BPC 157 and its role in accelerating musculoskeletal soft tissue healing.
9. **PMID —** (2025) — — Emerging Use of BPC-157 in Orthopaedic Sports Medicine: A Systematic Review.
10. **PMID —** (2026) — — Safety and Efficacy of Approved and Unapproved Peptide Therapies for Musculoskeletal Injuries and Athletic Performance

SOLANA SIGNATURE rYRKJgM4QKR1FhyPCEPGDSFs8PVy1MaDM1rf1pZ2kRvC8Wa1hBksqUsxMfCtR4vMWX5mU4nw8t2apa58SoPVYsS

DATA SHA-256 7cc81949f67a7d079a29e6d61b614925bdcc9e0778b9b71f11a81c3f96209c31

VERIFY https://solscan.io/tx/rYRKJgM4QKR1FhyPCEPGDSFs8PVy1MaDM1rf1pZ2kRvC8Wa1hBksqUsxMfCtR4vMWX5mU4nw8t2apa58SoPVYsS