

RESEARCH MONOGRAPH . COMPOUND PROFILE

Elabela

A 32-amino-acid secreted peptide hormone discovered in 2013 as the second endogenous ligand of the apelin receptor (APJ/APLNR), essential for vertebrate cardiovascular morphogenesis, human embryonic stem cell self-renewal, placental angiogenesis, and renal fluid homeostasis, with preclinical cardioprotective, renoprotective, antihypertensive, and neuroprotective activity across multiple disease models.

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ABSTRACT

Elabela (ELA), also designated Apela, Toddler, and Ende, is a secreted peptide hormone encoded by the APELA gene on human chromosome 4q32.3. The gene encodes a 54-amino-acid preproprotein containing a 22-residue signal peptide; cleavage yields the 32-amino-acid mature peptide ELA-32 (sequence QRPVNLTMRRLRKHNC LQRRCMPLHSRVPFP), which may be further processed by proprotein convertases to generate the bioactive isoforms ELA-21 and ELA-11 [1, 2]. Elabela was discovered independently by two groups in 2013 and 2014: Chng et al. (2013) identified the peptide in zebrafish as a hormone essential for heart development signaling through the apelin receptor (APLNR/APJ), while Pauli et al. (2014) characterized the same molecule as "Toddler," an embryonic signal promoting mesodermal cell migration [1, 3]. The peptide is the second endogenous ligand of the apelin receptor, a class A G-protein-coupled receptor previously known to bind only apelin; despite sharing a common receptor, Elabela and apelin exhibit less than 25 percent sequence similarity and display distinct spatiotemporal expression profiles and partially divergent signaling bias [4, 5]. Elabela activates the apelin receptor through Gi/o-coupled inhibition of adenylyl cyclase, stimulation of ERK1/2 and PI3K/AKT/mTOR pathways, mobilization of intracellular calcium, and recruitment of beta-arrestin, functioning as a balanced agonist across G-protein-dependent and beta-arrestin-dependent pathways [5, 6]. The binding affinity of ELA-32 for the human apelin receptor is high, with reported IC₅₀ values of approximately 0.27 nanomolar and K_d values of approximately 0.51 nanomolar [7]. Physiologically, Elabela is expressed at high

levels during embryogenesis across vertebrate species and in adult tissues with restricted distribution, principally kidney (collecting ducts and loops of Henle), prostate, and vascular endothelium [2, 8]. The peptide is essential for vertebrate cardiovascular development: genetic ablation of Elabela in zebrafish produces severe cardiac malformations including rudimentary or absent hearts, phenocopying loss of the apelin receptor itself [1]. In mice, Elabela knockout produces preeclampsia-like symptoms during pregnancy including proteinuria, hypertension, defective placental angiogenesis, and reduced fetal weight, effects that are rescued by exogenous ELA infusion [9]. A separate demonstration by Ho et al. (2015) established that Elabela is an endogenous growth factor sustaining human embryonic stem cell self-renewal via the PI3K/AKT pathway, with CRISPR-mediated deletion causing loss of pluripotency and cell death [10]. In the adult cardiovascular system, Elabela functions as an endogenous agonist of the apelin receptor producing positive inotropy, vasodilation, increased cardiac output, and depressor responses comparable to apelin; expression is downregulated in pulmonary arterial hypertension, and exogenous administration attenuates right ventricular hypertrophy and pulmonary vascular remodeling in monocrotaline-exposed rats [11]. Preclinical cardioprotective activity has been demonstrated across myocardial infarction, ischemia-reperfusion injury, and hypertensive cardiac fibrosis models, operating through PI3K/AKT-mediated anti-apoptotic, anti-fibrotic, and pro-angiogenic mechanisms [12, 13, 14]. Renoprotective activity is characterized by antagonism of the intrarenal renin-angiotensin system, reduction of blood pressure and albuminuria in salt-sensitive hypertensive rats, and prevention of vasopressin-induced aquaporin-2 translocation in collecting duct principal

cells, thereby promoting aqueous diuresis [15, 16].

Neuroprotective activity has been demonstrated in rodent models of ischemic stroke, where ELA attenuates neuronal apoptosis, ferroptosis, and pyroptosis through APJ-dependent signaling cascades [17, 18]. The in vitro plasma half-life of ELA-32 in human plasma is approximately 47 minutes, substantially longer than that of apelin-13 (approximately 5 minutes in vivo), though rapid degradation occurs in kidney homogenates (half-life approximately 44 seconds), and the short systemic half-life has motivated the development of Fc-fusion, PEGylated, and acylated analogs with extended duration of action [19, 20, 21]. No human clinical trials of exogenous Elabela administration have been completed as of the monograph revision date; the compound remains in the preclinical-to-translational research phase. This monograph reviews the chemistry, isoform biology, and synthesis of Elabela; the receptor pharmacology and signaling mechanisms in molecular detail; the pharmacokinetic profile including metabolism and stability-enhancement strategies; the preclinical evidence base across cardiovascular, renal, obstetric, stem cell, neurological, and oncological applications; sourcing and quality verification for research-grade material; reconstitution and handling; stack-interaction considerations; the adverse-event and safety signal from animal studies; and a comparative assessment of five apelinergic system candidates against Elabela on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Recommended name: Elabela.

Alternative names and synonyms: Apela, APELA, Toddler, Ende, ELA, ELA-32, ELA-21, ELA-11. The name "Elabela" was assigned by Chng et al. (2013) from the Malay word for "beautiful" in reference to the elegant cardiac phenotype of the zebrafish mutant [1]. The name "Toddler" was independently assigned by Pauli et al. (2014) in reference to the impaired gastrulation movements of zebrafish embryos lacking the peptide [3]. The International Union of Basic and Clinical Pharmacology (IUPHAR) recommends "Elabela/Toddler" as the formal designation for the second endogenous peptide ligand of the apelin receptor [4].

Gene symbol: APELA (approved by the HUGO Gene Nomenclature Committee). Former annotations: C4orf44, LOC100506013. The gene was originally classified as a noncoding transcript in genomic databases before functional characterization [1, 2].

Chromosomal location: Human chromosome 4q32.3.

Chemical Abstracts Service registry number: 1680205-79-1 (ELA-32, human mature peptide). CAS numbers for fragment isoforms include 1886973-05-2 (ELA-14, human) and 1784687-32-6 (ELA-11, human).

Online Mendelian Inheritance in Man (OMIM) entry: 615594.

UniProt accession: P0DMC3 (Homo sapiens APELA).

1.2 Structural class and chemistry

Elabela is a secreted peptide hormone of the apelinergic signaling system. It is classified as a micropeptide, a small open reading frame-encoded polypeptide that was initially overlooked by standard gene annotation pipelines owing to its short coding sequence [1, 2]. The structural class is distinct from the apelin peptide family:

despite sharing the apelin receptor as a common target, Elabela and apelin share less than 25 percent amino acid sequence identity, and their binding interactions with the receptor involve partially overlapping but distinct contact residues [4, 5].

Preproprotein sequence (human, 54 amino acids): MRFQQFLFAFFIFIMSLLLISGQRPVNLTMRRLKLRKHNCLQRRCMPLHSRVPFP. The 22-amino-acid N-terminal signal peptide (MRFQQFLFAFFIFIMSLLLISG) is cleaved during translocation into the endoplasmic reticulum to yield the 32-amino-acid mature secreted peptide [1, 2].

Mature peptide sequence (ELA-32, human): QRPVNLTMRRLKLRKHNCLQRRCMPLHSRVPFP (32 amino acids). The 13 C-terminal residues (CMPLHSRVPFP) are highly conserved across vertebrate species from zebrafish to human, indicating the receptor-binding pharmacophore resides in the C-terminal domain [2, 4].

Bioactive isoforms: ELA-32 may be further processed by proprotein convertases at dibasic cleavage sites (RR and KR motifs) to generate shorter bioactive isoforms: ELA-21 (C-terminal 21 residues), ELA-14 (C-terminal 14 residues with N-terminal pyroglutamate), and ELA-11 (C-terminal 11 residues) [4, 7]. All isoforms activate the apelin receptor, though with isoform-dependent differences in potency, efficacy, and signaling bias [5, 6].

Molecular weight: ELA-32: approximately 3,735 Da (human sequence, monoisotopic mass). ELA-21: approximately 2,528 Da. ELA-11: approximately 1,261 Da. Exact masses depend on post-translational modifications and counterion content in synthetic preparations.

Disulfide bond: ELA-32 contains two cysteine residues (Cys18 and Cys22 in the 32-residue numbering) that can form an intramolecular disulfide bond. The oxidized (disulfide) and reduced forms have been characterized; both retain receptor binding activity, though the relative contribution of the disulfide to in vivo stability and receptor interaction is a subject of ongoing investigation [4, 22].

Physical properties: White to off-white lyophilized powder in synthetic preparations. Soluble in water, phosphate-buffered saline, and dimethyl sulfoxide. The peptide is supplied as the trifluoroacetate salt from standard reverse-phase HPLC purification. Storage at minus 20 degrees Celsius or below in lyophilized form; aqueous solutions are stable for limited periods at 4 degrees Celsius.

1.3 Synthesis

Synthetic Elabela peptides (ELA-32, ELA-21, ELA-14, ELA-11) are produced by standard solid-phase peptide synthesis (SPPS) using Fmoc (9-fluorenylmethyloxycarbonyl) chemistry on Wang or Rink amide resin [7, 20]. The synthesis proceeds through iterative deprotection and coupling cycles for each amino acid residue, with standard activating reagents (HATU, HBTU, or DIC/Oxyma). The two cysteine residues in ELA-32 require orthogonal side-chain protection (typically trityl groups) to control disulfide bond formation during or after cleavage. Following global deprotection and cleavage from resin with trifluoroacetic acid/scavenger cocktails, the crude peptide is purified by preparative reverse-phase high-performance liquid chromatography to greater than 95 percent purity. Disulfide bond formation, when desired, is achieved by air oxidation in dilute aqueous buffer at pH 7.5 to 8.5 or by iodine-mediated oxidation. The product is characterized by analytical HPLC, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) or electrospray ionization mass spectrometry (ESI-MS), and amino acid analysis. Yields from SPPS are moderate for a 32-residue peptide (typically 15 to 30 percent overall from resin loading), with the principal synthetic challenges being the aggregation-prone central sequence and the methionine residue (Met8 in ELA-32) requiring oxidation prevention during synthesis and handling. Custom synthesis services are offered by multiple peptide chemistry vendors at milligram to gram scale.

2. Abstract

Elabela (ELA), the 32-amino-acid secreted peptide hormone encoded by the APELA gene, is the second endogenous ligand of the apelin receptor (APJ/APLNR), a widely expressed class A G-protein-coupled receptor of the apelinergic signaling system [1, 4]. Discovered independently in 2013 by Chng et al. in zebrafish embryonic development and in 2014 by Pauli et al. as "Toddler" in mesodermal cell migration, Elabela has emerged as a peptide of broad physiological significance across cardiovascular development, stem cell biology, renal homeostasis, placental function, and neuroprotection [1, 3, 10].

The principal distinguishing feature of Elabela relative to apelin is its developmental essentiality: genetic ablation of Elabela in zebrafish produces severe cardiac malformations including cardia bifida and rudimentary hearts, whereas apelin knockout zebrafish develop normally [1]. In mice, Elabela but not apelin knockout produces preeclampsia-like symptoms during pregnancy, including hypertension, proteinuria, and defective placental angiogenesis, establishing Elabela as the non-redundant endogenous ligand for APJ-dependent developmental and obstetric programs [9]. A third developmental function was characterized by Ho et al. (2015), who demonstrated that Elabela is an endogenous growth factor secreted by human embryonic stem cells that sustains self-renewal through PI3K/AKT/mTOR pathway activation [10].

In the adult cardiovascular system, Elabela acts as an endogenous positive inotrope and vasodilator through APJ activation, with expression downregulated in pulmonary arterial hypertension and heart failure [11]. Preclinical studies have demonstrated cardioprotective activity in myocardial infarction, ischemia-reperfusion injury, and pressure-overload heart failure models, mediated through PI3K/AKT anti-apoptotic signaling, ERK/HIF-1alpha/VEGF pro-angiogenic pathways, and IL-6/STAT3/GPX4 anti-ferroptotic mechanisms [12, 13, 14]. Renoprotective activity operates through antagonism of the intrarenal renin-angiotensin system, with exogenous ELA-32 infusion lowering blood pressure, reducing albuminuria, and blocking inflammatory and fibrotic injury markers in salt-sensitive hypertensive rats [15, 16]. Neuroprotective activity has been demonstrated in rodent ischemic stroke models, where ELA attenuates neuronal apoptosis, ferroptosis, and pyroptosis through APJ-dependent downstream signaling [17, 18].

The compound binds the human apelin receptor with high affinity (IC₅₀ approximately 0.27 nM; K_d approximately 0.51 nM for ELA-32) and activates both Gi/o-protein-dependent and beta-arrestin-dependent pathways, functioning as a balanced agonist in contrast to the more beta-arrestin-biased profiles observed with some apelin isoforms [5, 6, 7]. The in vitro plasma half-life of ELA-32 is approximately 47 minutes, longer than that of apelin-13, but rapid kidney degradation and the absence of oral bioavailability have constrained translational development and motivated engineering of Fc-fusion, PEGylated, and acylated analogs [19, 20, 21].

No human clinical trials of exogenous Elabela administration have been completed. The compound is in the preclinical-to-translational research phase with active investigation as a potential therapeutic for heart failure, pulmonary arterial hypertension, preeclampsia, acute kidney injury, and ischemic stroke. Research-grade synthetic ELA-32 and fragment isoforms are available from peptide chemistry suppliers for in vitro and in vivo investigation.

3. Discovery and Development History

3.1 Origin and independent discovery

Elabela was discovered through two independent forward genetic and bioinformatic approaches in zebrafish. Chng et al. (2013) at the Institute of Medical Biology, A*STAR, Singapore, identified the APELA gene through a screen for secreted factors required for zebrafish heart development [1]. The gene had been annotated as a noncoding transcript (LOC100506013 in human, C4orf44 in some databases) owing to its short open reading frame (54 codons), which fell below the 100-codon threshold used by standard gene prediction algorithms. Chng et al. demonstrated that the encoded 32-amino-acid mature peptide was secreted, signaled through the apelin receptor (APLNR/APJ), and was essential for cardiac progenitor cell migration and heart tube formation. They named the peptide "Elabela" from the Malay word for "beautiful" [1].

Independently, Pauli et al. (2014) at the Max Planck Institute of Molecular Cell Biology and Genetics in Dresden and at Yale University identified the same gene product through a ribosome profiling screen for translated small open reading frames in zebrafish embryos [3]. They named the peptide "Toddler" in reference to the characteristic gastrulation movement defects in loss-of-function embryos. The Pauli et al. study characterized Toddler as a secreted signal that promotes cell movement via apelin receptors during gastrulation, establishing the peptide as essential for mesodermal cell migration independent of its later cardiac role [3].

The convergence of these two independent discoveries from different biological entry points (cardiac development and gastrulation) established Elabela/Toddler as a bona fide endogenous ligand of the apelin receptor with non-redundant developmental functions distinct from those of apelin.

3.2 Recognition as the second endogenous APJ ligand

Prior to the discovery of Elabela, the apelin receptor (first cloned in 1993 by O'Dowd et al. as an orphan receptor designated APJ) was thought to have only one endogenous peptide ligand: apelin, identified in 1998 by Tatemoto et al. from bovine stomach extracts [23, 24]. The International Union of Basic and Clinical Pharmacology

(IUPHAR) formally recommended in 2019 that Elabela/Toddler be designated as the second endogenous peptide ligand of the apelin receptor, based on the accumulated evidence of endogenous expression, receptor activation, and physiological function [4].

3.3 Expansion of the research literature

The year following initial discovery saw rapid expansion of the Elabela research literature across several domains. Wang et al. (2015) confirmed that the Elabela-apelin receptor signaling pathway is functional in mammalian systems, demonstrating receptor activation in Chinese hamster ovary cells stably expressing human APJ [6]. Ho et al. (2015) identified Elabela as an endogenous growth factor for human embryonic stem cell self-renewal, extending the biology from zebrafish development to mammalian stem cell biology [10]. Hassan et al. (2015) characterized the hormonal peptide Elabela as a guide for angioblast migration to the midline during vasculogenesis [25].

Ho et al. (2017) published a landmark study in *Science* demonstrating that ELABELA deficiency promotes preeclampsia and cardiovascular malformations in mice, establishing the first mammalian loss-of-function phenotype and directly linking the peptide to a human disease of major clinical significance [9]. Yang et al. (2017) published in *Circulation* the demonstration that Elabela is an endogenous agonist of the apelin receptor in the adult cardiovascular system, with expression downregulated in pulmonary arterial hypertension and therapeutic efficacy of exogenous administration in a rat monocrotaline model [11].

Subsequent years produced an expanding preclinical literature on cardioprotection (myocardial infarction, ischemia-reperfusion, heart failure), renoprotection (acute kidney injury, hypertensive nephropathy, diabetic kidney disease), neuroprotection (ischemic stroke), and oncology (ovarian cancer, renal cell carcinoma, glioma, chronic lymphocytic leukemia) [12, 13, 14, 15, 17, 26, 27]. Modified analogs with extended half-lives (Fc-ELA-21 fusion protein, PEGylated and acylated ELA derivatives) were developed beginning in 2019 to address the translational limitation of the short in vivo half-life [19, 20, 21].

3.4 Current development status

As of the monograph revision date, no human clinical trials of exogenous Elabela administration have been registered or completed. The compound remains in the preclinical research phase, with active investigation across cardiovascular, renal, obstetric, neurological, and oncological domains. Circulating Elabela levels have been measured in human clinical cohorts as a potential diagnostic or prognostic biomarker in heart failure, preeclampsia, chronic kidney disease, and several cancer types, but these are observational biomarker studies rather than therapeutic interventional trials [28, 29]. The translational path forward depends on the development of metabolically stable analogs or delivery systems that overcome the rapid in vivo degradation of the native peptide.

4. Mechanism of Action

Elabela is an endogenous peptide agonist of the apelin receptor (APJ/APLNR), a class A (rhodopsin-like) G-protein-coupled receptor of the apelinergic signaling system. The receptor and its two known endogenous ligands (apelin and Elabela) constitute a spatiotemporal dual-ligand system with overlapping but distinct physiological functions [4, 5].

4.1 Apelin receptor binding and activation

The apelin receptor is a seven-transmembrane domain GPCR coupled predominantly to Gi/o and Gq heterotrimeric G proteins. It is expressed at high density in the cardiovascular system (cardiomyocytes, vascular endothelium, vascular smooth muscle), the kidney (collecting duct principal cells, glomerular endothelium, proximal tubule), the central nervous system (hypothalamus, cortex, hippocampus), the placenta, the lung, and the gastrointestinal tract [4].

ELA-32 binds the apelin receptor with high affinity: the IC₅₀ for displacement of [125I]-apelin-13 is approximately 0.27 nanomolar, and the equilibrium dissociation constant (K_d) determined by radioligand binding is approximately 0.51 nanomolar [7, 11]. In silico molecular modeling indicates that Elabela and apelin share overlapping binding sites within the receptor orthosteric pocket, with the conserved C-terminal residues of ELA (CMPLHSRVFPF) occupying the deep transmembrane binding cavity analogous to the C-terminal RPR motif of apelin [4, 11]. However, the N-terminal regions of the two peptides engage distinct extracellular loop contacts, contributing to the partially divergent signaling profiles observed between the two ligands.

4.2 G-protein-dependent signaling

Activation of the apelin receptor by Elabela engages canonical Gi/o-dependent signaling cascades [5, 6]:

Inhibition of adenylyl cyclase, producing dose-dependent suppression of intracellular cyclic AMP (cAMP) accumulation. This is the canonical readout of Gi/o coupling and is observed with all bioactive Elabela isoforms (ELA-32, ELA-21, ELA-11)

with isoform-dependent potency.

Activation of extracellular signal-regulated kinases 1 and 2 (ERK1/2) through Gi/o-derived betagamma subunit-dependent Ras/Raf/MEK pathway activation. ERK1/2 activation mediates proliferative, pro-survival, and pro-angiogenic downstream effects.

Activation of phosphoinositide 3-kinase (PI3K) and the downstream AKT/mTOR signaling axis, producing anti-apoptotic (BAD phosphorylation, caspase inhibition), pro-survival (mTORC1 activation, p70S6K phosphorylation), and metabolic (glucose uptake, protein translation) effects [10, 12].

Mobilization of intracellular calcium through Gq/11-dependent phospholipase C activation, producing rapid transient calcium elevations in cardiomyocytes and endothelial cells.

4.3 Beta-arrestin-dependent signaling

Elabela activation of the apelin receptor produces recruitment of beta-arrestin 1 and beta-arrestin 2, followed by receptor internalization through clathrin-coated pit endocytosis [5, 6]. The beta-arrestin-dependent signaling arm mediates receptor desensitization, endosomal signaling, and scaffolding of additional signaling complexes including the AP2 clathrin adaptor.

Comparative signaling bias studies have demonstrated that Elabela isoforms exhibit distinct bias profiles relative to apelin isoforms. ELA-32 shows balanced agonism across G-protein and beta-arrestin pathways, while ELA-21 exhibits preferential activity on the G-protein-dependent pathway [5]. In contrast, some apelin isoforms (notably [Pyr1]-apelin-13) show more pronounced beta-arrestin recruitment relative to G-protein activation. The signaling bias has implications for the design of therapeutic analogs, as G-protein-biased agonists may produce sustained beneficial cardiovascular effects with reduced receptor desensitization [5, 30].

4.4 Downstream effector pathways in specific tissues

Cardiovascular system: In cardiomyocytes, ELA-mediated PI3K/AKT activation produces positive inotropy (increased contractility through enhanced calcium handling and sarcomeric protein phosphorylation), anti-apoptotic signaling (reduced caspase-3 activation, increased Bcl-2/Bax ratio), and anti-fibrotic effects (reduced

TGF-beta/Smad signaling, decreased collagen deposition) [12, 13]. In vascular endothelium, ERK/HIF-1alpha/VEGF pathway activation promotes angiogenesis and endothelial survival [14]. ELA also modulates the IL-6/STAT3/GPX4 axis to prevent ferroptosis in hypertensive cardiac remodeling [31].

Kidney: In collecting duct principal cells, ELA/APJ signaling opposes vasopressin-induced translocation of aquaporin-2 (AQP2) water channels to the apical membrane, promoting aqueous diuresis and contributing to body fluid homeostasis [16]. In the intrarenal renin-angiotensin system, ELA functions as a counterregulatory "Yang" peptide opposing the prorenin receptor/soluble prorenin receptor "Yin" axis: ELA blocks prorenin receptor expression and reduces intrarenal angiotensin II, renin, and prorenin levels, producing blood pressure reduction and renoprotection [15].

Central nervous system: In ischemic stroke models, ELA-mediated APJ activation upregulates miR-124-3p, which targets CTDSBP1 to activate AKT signaling and suppress neuronal apoptosis [17]. ELA also inhibits neuronal ferroptosis through APJ-dependent oxidative stress regulation and prevents pyroptosis through APJ/ZBP1 signaling modulation [18, 32].

Stem cells: In human embryonic stem cells, ELA acts in an auto/paracrine fashion through APJ to activate PI3K/AKT/mTORC1 signaling, promoting cell-cycle progression, protein translation, and blocking stress-induced apoptosis. ELA partially replaces the requirement for exogenous insulin in stem cell culture but is functionally non-redundant with insulin, additionally poising cells toward mesendoderm lineage commitment [10].

Placenta: ELA promotes extravillous trophoblast differentiation and placental angiogenesis through APJ-dependent signaling. ELA deficiency produces defective syncytiotrophoblast differentiation, increased placental cell death, reduced labyrinth vascularization, and elevated placental HIF-1alpha, recapitulating key features of preeclampsia pathogenesis [9, 33].

4.5 Receptor-independent signaling

Some reports have suggested that Elabela may also exert biological effects through receptor-independent mechanisms, potentially including direct interactions with cell surface proteoglycans or intracellular targets, though these findings remain

preliminary and the overwhelming preponderance of characterized Elabela biology is APJ-dependent [4, 34].

5. Pharmacokinetics and Routes of Administration

5.1 Endogenous expression and circulating levels

Elabela is expressed at high levels during embryogenesis across vertebrate species, where it is present in undifferentiated embryonic cells, the developing cardiovascular system, and the gastrointestinal endoderm [1, 3]. In adult humans, APELA mRNA expression is restricted, with the highest transcript levels detected in kidney (collecting ducts and loops of Henle), prostate, and vascular endothelium [2, 8]. The placenta produces Elabela during pregnancy, though human studies have questioned whether the placenta is the major source of circulating ELA in pregnancy [33, 35].

Circulating Elabela levels in healthy adult humans have been measured by enzyme-linked immunosorbent assay (ELISA) at concentrations in the low nanomolar to picomolar range, though absolute values vary substantially across assay platforms and study populations [28, 29]. Levels are reportedly reduced in patients with heart failure, essential hypertension, and some cancer types, suggesting potential utility as a diagnostic or prognostic biomarker [28, 29, 36].

5.2 Exogenous administration and absorption

Elabela is a peptide and is not orally bioavailable in its native form. Exogenous administration in preclinical studies has used intravenous bolus injection, intravenous infusion, subcutaneous injection, and osmotic minipump infusion [11, 12, 15]. Intraperitoneal injection has been used in rodent studies of neuroprotection [17, 18]. The absence of oral bioavailability is a fundamental constraint on clinical translation and a principal motivation for the development of modified analogs.

5.3 Distribution

No formal volume of distribution studies have been published for exogenous ELA-32 in any species. The peptide is expected to distribute principally within the extracellular fluid compartment and to bind with high affinity to APJ-expressing tissues

(cardiovascular system, kidney, central nervous system). Plasma protein binding has not been formally characterized for ELA-32 but is expected to be moderate based on the peptide's charge distribution and molecular weight.

5.4 Metabolism and stability

The in vitro metabolism of synthetic ELA-32 has been characterized in human plasma and kidney homogenates by Murza et al. (2021) [19]. Key findings are:

Plasma stability: The half-life of ELA-32 in human plasma at 37 degrees Celsius is approximately 47.2 minutes (standard deviation 5.7 minutes), with greater than 20 percent of the parent peptide still detectable after 240 minutes of incubation. This plasma stability is substantially greater than that of apelin-13 (which has an in vivo half-life of approximately 5 minutes, limited primarily by angiotensin-converting enzyme 2, ACE2, cleavage of the C-terminal phenylalanine) [19, 37].

Kidney stability: In contrast to its moderate plasma stability, ELA-32 is rapidly degraded in human kidney homogenates, with a half-life of approximately 44 seconds and complete disappearance of the parent peptide within 20 minutes [19]. The rapid renal degradation is attributed to the high density of membrane-bound peptidases in the proximal tubule and collecting duct.

Metabolite identification: The major metabolites identified after incubation in human plasma are ELA-16 and ELA-11, generated by cleavage at the dibasic cleavage sites. ELA-21 was not identified as a major plasma metabolite in this in vitro system. ELA-16 was proposed as a potentially more stable bioactive fragment with implications for endogenous peptide processing [19].

Enzymatic degradation: The principal enzymes responsible for ELA degradation in vivo have not been fully characterized. Unlike apelin-13, ELA-32 does not contain the C-terminal phenylalanine-proline motif that is the canonical ACE2 cleavage site, suggesting that the metabolic fate of ELA-32 is distinct from that of apelin and involves different peptidase activities [4, 19].

5.5 Stability-enhanced analogs

The short in vivo half-life of native ELA peptides has motivated the development of modified analogs with extended duration of action:

Fc-ELA-21 fusion protein: Peng et al. (2019) constructed a recombinant fusion of ELA-21 with the Fc fragment of human immunoglobulin G1, producing a chimeric protein with a circulating half-life of approximately 44 hours in mice after subcutaneous injection, approximately 500-fold longer than the estimated in vivo half-life of the native peptide [20]. The Fc-ELA-21 fusion retained apelin receptor agonist activity and mitigated post-infarct heart dysfunction in a rat coronary artery ligation model. A subsequent study (2025) confirmed that Fc-Elabela mitigates heart failure without liver and renal toxicity in mice [38].

PEGylated and acylated analogs: Sato et al. (2021) reported PEGylated and acylated Elabela analogs with enhanced receptor binding affinity, prolonged plasma stability (half-life extended to several hours), and protective efficacy in a mouse model of acute kidney injury [21]. These modifications reduced enzymatic degradation while preserving receptor activation.

Macrocyclic analogs: Structure-activity relationship studies have explored macrocyclic constraints on the Elabela C-terminal pharmacophore to improve metabolic stability and receptor residence time [30].

5.6 Routes of administration in preclinical studies

Intravenous infusion (continuous, by osmotic minipump) is the most common route for chronic cardiovascular studies, typically at doses of 2 to 5 micrograms per kilogram per hour in rats [11, 15]. Intravenous bolus and intraperitoneal injection are used for acute studies. Subcutaneous injection has been used for Fc-fusion protein delivery. Intracerebroventricular injection has been used in limited neuroprotection studies to establish central nervous system-specific effects.

6. Preclinical Pharmacology

6.1 Cardiovascular protection

Myocardial infarction: Exogenous ELA-32 administration by intravenous infusion beginning at the time of coronary artery ligation in rats significantly reduced infarct size, improved left ventricular ejection fraction, reduced serum markers of myocardial injury (lactate dehydrogenase, creatine kinase-MB, troponin I), and suppressed markers of oxidative stress at 2 weeks post-infarction [12]. The cardioprotective mechanism involved PI3K/AKT pathway activation, increased Bcl-2 expression, reduced Bax expression, and suppressed caspase-3 activation, consistent with an anti-apoptotic mechanism.

Ischemia-reperfusion injury: In Wistar rat models of myocardial ischemia-reperfusion, ELA treatment attenuated injury through dual mechanisms: activation of the ERK/HIF-1 α /VEGF pathway to promote angiogenesis in the peri-infarct zone, and PI3K/AKT-mediated inhibition of mitochondrial dysfunction and apoptosis [13, 14]. Collagen fiber deposition (a marker of cardiac fibrosis) was significantly reduced in ELA-treated animals compared to vehicle controls.

Heart failure and hypertensive cardiomyopathy: ELA alleviates ferroptosis, myocardial remodeling, fibrosis, and cardiac dysfunction in angiotensin II-infused hypertensive mice by modulating the IL-6/STAT3/GPX4 signaling pathway [31]. Sato et al. (2021) demonstrated that Fc-ELA-21 administration improved cardiac function and reduced cardiac fibrosis in a post-infarction heart failure model without hepatic or renal toxicity [20, 38].

Pulmonary arterial hypertension: Yang et al. (2017) demonstrated that ELA expression is downregulated in lung and right ventricular tissue from patients with pulmonary arterial hypertension and from monocrotaline-treated rats [11]. Exogenous ELA-32 infusion attenuated monocrotaline-induced right ventricular systolic pressure elevation, right ventricular hypertrophy, and pulmonary vascular remodeling. In isolated heart preparations, ELA produced acute positive inotropy, increased cardiac output, and vasodilation comparable in magnitude to equimolar apelin [11].

6.2 Renal protection

Salt-sensitive hypertension: Deng et al. (2020) demonstrated that exogenous ELA-32 infusion in high-salt-loaded Dahl salt-sensitive rats significantly lowered blood pressure and albuminuria [15]. The mechanism involved suppression of intrarenal renin-angiotensin system components: urinary soluble renin receptor (sPRR), angiotensin II, and prorenin/renin excretion were all reduced by ELA infusion. High-salt-induced upregulation of inflammatory cytokines (TNF-alpha, IL-6), fibrosis markers (TGF-beta, collagen I), and kidney injury markers (NGAL, KIM-1) were markedly attenuated.

Acute kidney injury: PEGylated and acylated ELA analogs demonstrated renoprotective efficacy in cisplatin-induced and ischemia-reperfusion-induced acute kidney injury models in mice, reducing serum creatinine, blood urea nitrogen, and tubular necrosis scores [21].

Diabetic kidney disease: ELA signaling through the PI3K/AKT/mTOR pathway has been reported to reduce apoptosis and promote survival in diabetic kidney models, though the evidence base is principally from in vitro and early in vivo studies [39].

Fluid homeostasis: In the collecting duct, ELA/APJ signaling opposes vasopressin-induced AQP2 trafficking to the apical membrane, promoting free water excretion and contributing to the diuretic and antihypertensive profile [16].

6.3 Preeclampsia

Ho et al. (2017) demonstrated that ELABELA knockout pregnant mice develop preeclampsia-like symptoms including proteinuria, elevated blood pressure beginning at embryonic day 16 with resolution at parturition, defective placental angiogenesis with reduced labyrinth vascularization, increased placental cell death, reduced syncytiotrophoblast differentiation, and reduced fetal weight [9]. Infusion of exogenous ELA into Elabela-knockout pregnant mice normalized hypertension, proteinuria, and birth weight, establishing proof-of-concept for ELA as a potential therapeutic in preeclampsia [9]. Notably, apelin knockout pregnant mice did not develop preeclampsia, confirming the non-redundant essential role of Elabela in placental vascular development. Subsequent studies demonstrated that ELA enhances extravillous trophoblast differentiation through the MEK/ERK axis in human trophoblast cell lines [33, 40].

The clinical translation of these findings remains uncertain. Ho et al. (2018) reported that circulating ELABELA levels and placental ELABELA mRNA were not significantly different between preeclamptic and normotensive pregnancies in a human cohort of 82 matched pairs, suggesting that the murine preeclampsia phenotype may not directly recapitulate the dominant pathophysiology of human preeclampsia [35].

6.4 Neuroprotection

Ischemic stroke: Intranasal or intraperitoneal ELA administration in mouse models of middle cerebral artery occlusion reduced infarct volume, improved neurological deficit scores, and attenuated neuronal apoptosis through APJ/miR-124-3p/CTDSP1/AKT pathway activation [17]. ELA also inhibited neuronal ferroptosis (an iron-dependent form of programmed cell death) through APJ-dependent modulation of oxidative stress [18]. A third neuroprotective mechanism involves ELA-mediated inhibition of neuronal pyroptosis and mitochondrial fission through APJ/ZBP1 signaling [32].

6.5 Stem cell biology

Ho et al. (2015) demonstrated that ELA is constitutively secreted by human embryonic stem cells and acts in an auto/paracrine manner through APJ to sustain self-renewal [10]. CRISPR/Cas9-mediated APELA deletion, shRNA knockdown, or neutralizing antibody treatment caused reduced hESC growth, increased cell death, and loss of pluripotency markers. Mechanistically, ELA activated PI3K/AKT/mTORC1 signaling, promoted cell-cycle progression and protein translation, and blocked stress-induced apoptosis. ELA partially replaced the need for exogenous insulin in hESC culture medium but was functionally non-redundant with insulin; unlike insulin, ELA poised hESCs toward the mesendoderm lineage, indicating a dual function in maintaining stemness and facilitating lineage commitment [10].

6.6 Oncology

The role of Elabela in cancer biology is complex and context-dependent [26, 27]. In ovarian clear cell carcinoma (OCCC), ELA stimulates proliferation and migration, and disruption of Elabela expression reduces OCCC tumorigenesis in xenograft models, suggesting a pro-tumorigenic role [26]. In renal cell carcinoma, mTORC1 signaling mediates an ELA-dependent growth suppression, and ELA and sunitinib

show synergistic anti-tumor and anti-angiogenic effects [27]. In chronic lymphocytic leukemia, elevated plasma ELA levels correlate with disease prognosis and treatment response [41]. In glioma and thyroid cancer, the ELA/APJ axis has been characterized in expression studies but functional roles remain under investigation [26]. The dual pro- and anti-tumorigenic activities of ELA across cancer types reflect the context-dependent nature of apelinergic signaling and the intersection of the APJ pathway with fundamental cell survival (PI3K/AKT) and angiogenic (VEGF) programs.

7. Clinical Evidence Base

7.1 Absence of therapeutic clinical trials

No interventional clinical trials of exogenous Elabela administration in humans have been registered or completed as of the monograph revision date. The compound has not entered Phase 1 human pharmacokinetic or safety studies. The translational path is constrained by the short in vivo half-life of native ELA peptides and the ongoing development of metabolically stable analogs suitable for human administration.

7.2 Human biomarker and observational studies

Multiple clinical studies have measured circulating Elabela levels as a potential diagnostic or prognostic biomarker:

Heart failure: Circulating ELA levels are reportedly reduced in patients with heart failure compared to healthy controls, with some studies reporting correlations between ELA levels and New York Heart Association functional class, left ventricular ejection fraction, and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels [28, 36]. These observations are consistent with the animal model evidence of ELA downregulation in cardiac disease states.

Hypertension: Reduced circulating ELA levels have been reported in patients with essential hypertension compared to normotensive controls, supporting the hypothesis that ELA deficiency contributes to the pathogenesis of hypertension through loss of APJ-mediated vasodilation and diuresis [29].

Preeclampsia: The relationship between circulating ELA and preeclampsia in humans is inconsistent. Ho et al. (2018) reported no significant difference in circulating ELABELA levels or placental ELABELA mRNA between preeclamptic and normotensive pregnancies [35]. Other groups have reported reduced circulating ELA in early-onset preeclampsia, and the discordance may reflect differences in assay methodology, gestational timing, and preeclampsia subtypes.

Chronic kidney disease: Limited observational data suggest altered circulating ELA levels in chronic kidney disease, consistent with the high expression of APELA in renal tissue and the renoprotective preclinical profile [39].

Cancer: Elevated or altered circulating ELA levels have been reported in chronic lymphocytic leukemia, ovarian cancer, and other malignancies, though the biomarker studies are small and require replication [26, 41].

7.3 Circulating ELA as a biomarker for aging

Zhong et al. (2023) characterized Elabela as a promising preventive/diagnostic biomarker for age-related diseases, noting associations between declining ELA levels and cardiovascular aging, renal functional decline, and metabolic dysfunction in observational cohorts [42]. These associations are correlational and do not establish causation; interventional studies in humans are needed to determine whether ELA supplementation modifies age-related disease trajectories.

8. Sourcing and Quality Verification

Research-grade synthetic Elabela peptides are available from multiple peptide chemistry and pharmacological reagent suppliers. The principal commercially available isoforms are:

ELA-32 (human): Full-length mature peptide, 32 amino acids, CAS 1680205-79-1. Previously available from Tocris Bioscience (Cat. No. 6291; now discontinued at that supplier), Phoenix Pharmaceuticals, MedChemExpress, Bachem, AnaSpec, and custom peptide synthesis services. Purity greater than 95 percent by HPLC is standard for research-grade material.

ELA-21 (human): C-terminal 21-residue fragment. Available from multiple suppliers. Isoform-specific biological activity requires characterization in the investigator's assay system.

ELA-14 (human): C-terminal 14-residue fragment with N-terminal pyroglutamate, CAS 1886973-05-2. Available from Tocris (Cat. No. 6293) and other suppliers.

ELA-11 (human): C-terminal 11-residue fragment, CAS 1784687-32-6. Available from Tocris (Cat. No. 6698) and other suppliers.

ELA RR>GG mutant: A receptor-activation-deficient mutant (Arg-Arg to Gly-Gly substitution) used as a negative control in signaling studies. Available from Tocris (Cat. No. 6292).

Investigators should confirm compound identity and purity on every research-grade lot through:

- Analytical HPLC confirming purity greater than 95 percent by peak area
- Mass spectrometry (MALDI-TOF or ESI-MS) confirming exact molecular weight within 1 Da of the theoretical value for the specified isoform
- Amino acid analysis confirming composition consistent with the target sequence
- Bioactivity confirmation in a functional assay (e.g., cAMP inhibition or ERK phosphorylation in APJ-expressing cells) on representative lots

- Counterion analysis (trifluoroacetate content) if gravimetric peptide quantification is critical for dose-response accuracy

Pricing for research-grade ELA-32 is moderate to high for a synthetic peptide, typically in the range of \$200 to \$500 per milligram at research quantities from established suppliers. Custom synthesis of gram-scale quantities is available from contract peptide synthesis organizations at negotiated pricing.

9. Reconstitution and Handling

Synthetic Elabela peptides are supplied as lyophilized powders, typically as the trifluoroacetate salt. Reconstitution and handling procedures are standard for research-grade synthetic peptides with the following specific considerations:

Reconstitution solvent: Sterile deionized water or phosphate-buffered saline (pH 7.4) is the recommended reconstitution solvent for in vivo and cell-based studies. Dimethyl sulfoxide (DMSO) may be used for concentrated stock solutions intended for in vitro receptor binding and signaling assays; the final DMSO concentration in the assay should be kept below 0.1 percent to avoid vehicle effects on cell signaling.

Stock solution concentration: Prepare stock solutions at 1 to 10 mg/mL (approximately 270 micromolar to 2.7 millimolar for ELA-32). Vortex gently until complete dissolution. Do not use sonication, which may damage the peptide.

Aliquoting: Divide stock solutions into single-use aliquots immediately after reconstitution to avoid repeated freeze-thaw cycles. Store aliquots at minus 20 degrees Celsius for short-term use (up to 1 month) or minus 80 degrees Celsius for long-term storage.

Stability considerations: The methionine residue at position 8 of ELA-32 is susceptible to oxidation; avoid prolonged exposure to air, light, or oxidizing agents during handling. The cysteine residues at positions 18 and 22 are susceptible to non-specific disulfide formation with other thiol-containing species; include reducing agents (dithiothreitol, 1 mM) in buffers if the reduced form is required, or allow controlled air oxidation for the intramolecular disulfide form. Aqueous solutions at neutral pH are stable for up to 24 hours at room temperature and up to 7 days at 4 degrees Celsius based on in vitro stability data; use within these timeframes for quantitative studies [19].

Lyophilized storage: Store lyophilized peptide at minus 20 degrees Celsius or below in the original sealed container with desiccant. The lyophilized material is stable for at least 12 months under these conditions.

Endotoxin considerations: For in vivo studies, confirm that the synthetic peptide preparation is endotoxin-free (less than 0.1 EU/mL at working concentration) to avoid confounding inflammatory responses, particularly in cardiovascular and renal protection studies where NF-kappaB pathway activation is a relevant readout.

10. Stack Interaction Considerations

Investigators conducting research with Elabela, especially in chronic dosing regimens or in combination with other research compounds, should consider the following pharmacological interactions:

Apelin and apelin receptor agonists: Concurrent administration of Elabela with apelin peptides (apelin-13, [Pyr1]-apelin-13, apelin-17, apelin-36) produces additive or potentially synergistic effects at the APJ receptor. The two peptides may compete for the same orthosteric binding site; the interaction kinetics depend on the relative concentrations and binding affinities of the co-administered isoforms. Combination studies are informative for understanding the spatiotemporal dual-ligand system but require careful dose-response characterization.

Apelin receptor antagonists: ML221 (the principal small-molecule APJ antagonist) and the competitive peptide antagonist [Ala13]-apelin-13(F13A) block ELA-mediated APJ activation and are used as pharmacological tools to confirm APJ dependence of observed biological effects [4].

Renin-angiotensin system modulators: ELA antagonizes the intrarenal renin-angiotensin system [15]. Concurrent administration with ACE inhibitors (enalapril, ramipril), angiotensin receptor blockers (losartan, valsartan), or direct renin inhibitors (aliskiren) may produce additive antihypertensive and renoprotective effects. The combination has not been systematically characterized in preclinical models but is physiologically plausible based on the opposing regulatory relationships between the apelinergic and RAS systems.

Vasopressin and aquaporin modulators: ELA opposes vasopressin-induced AQP2 trafficking in the collecting duct [16]. Concurrent administration with desmopressin (synthetic vasopressin analog) may produce pharmacological antagonism of the antidiuretic response. Conversely, concurrent administration with vaptans (tolvaptan, conivaptan) may produce additive aquaretic effects.

Inotropic agents: ELA produces positive inotropy through APJ/Gi/PI3K/AKT-dependent mechanisms [11]. Concurrent administration with other positive inotropes (dobutamine, milrinone, digoxin) may produce additive contractile effects. The hemodynamic interaction has not been characterized.

PI3K/AKT pathway modulators: Concurrent administration of ELA with PI3K inhibitors (wortmannin, LY294002, PI3K-alpha-selective inhibitors) or AKT inhibitors (MK-2206) abolishes the downstream protective signaling and is used experimentally to confirm pathway dependence. mTOR inhibitors (rapamycin, everolimus) block ELA-mediated mTORC1 activation and the associated stem cell self-renewal and anti-apoptotic effects [10].

Peptidase inhibitors: Concurrent administration with neprilysin inhibitors (sacubitril, as in the sacubitril/valsartan combination) may extend the effective half-life of ELA by reducing peptidase-mediated degradation, analogous to the established effect of neprilysin inhibition on natriuretic peptide levels. This interaction has not been specifically characterized for ELA but is mechanistically plausible.

11. Adverse Events and Safety Signal

11.1 General safety profile from animal studies

The overall safety profile of exogenous Elabela administration in preclinical studies is favorable, consistent with the peptide's identity as an endogenous hormone administered at physiological or modestly supraphysiological concentrations. No formal toxicology studies with Good Laboratory Practice compliance have been published.

The principal observations from the preclinical literature are:

Hemodynamic effects: ELA produces vasodilation and blood pressure reduction through APJ-mediated mechanisms [11, 15]. At supraphysiological doses, these effects could theoretically produce hypotension, though no reports of dose-limiting hypotension have appeared in the published animal literature at the doses used in efficacy studies (typically 2 to 5 micrograms per kilogram per hour by continuous infusion in rats).

Cardiac effects: ELA produces positive inotropy at pharmacological concentrations [11]. Excessive inotropic stimulation could theoretically produce arrhythmia or myocardial energy depletion, though no such adverse events have been reported at efficacy doses. The distinction between the beneficial positive inotropic effect in heart failure and the potentially detrimental effect of excessive stimulation has not been delineated by formal dose-response toxicity studies.

Hepatic and renal safety: The Fc-Elabela fusion protein study (2025) specifically assessed hepatic and renal safety biomarkers in mice with post-infarction heart failure and reported that Fc-Elabela mitigated heart failure without liver and renal toxicity [38]. Serum alanine aminotransferase, aspartate aminotransferase, creatinine, and blood urea nitrogen were not elevated by Fc-ELA treatment relative to vehicle controls.

11.2 Theoretical safety considerations

Angiogenic potential: ELA promotes angiogenesis through ERK/HIF-1alpha/VEGF signaling [14]. In the context of solid tumors, exogenous ELA administration could theoretically promote tumor angiogenesis and growth, as suggested by the pro-tumorigenic activity observed in ovarian clear cell carcinoma models [26]. This concern is speculative for systemic administration at the doses used in cardiovascular and renal protection studies but warrants consideration in the design of chronic dosing studies.

Stem cell and proliferative effects: ELA promotes cell-cycle progression and mTORC1 activation [10]. Long-term administration could theoretically promote proliferative disorders, though no such signal has been observed in published studies of up to several weeks' duration.

Immunogenicity (modified analogs): Fc-fusion proteins, PEGylated peptides, and other modified analogs carry the theoretical risk of anti-drug antibody formation on chronic administration. The Fc-ELA-21 fusion protein studies have not reported immunogenicity data from chronic dosing experiments.

11.3 Species-specific considerations

The preclinical safety literature is derived principally from rats and mice. Larger-animal pharmacology and toxicology studies (dog, non-human primate) have not been published for Elabela. Species differences in APJ expression density, Elabela metabolism, and hemodynamic sensitivity should be considered in extrapolating rodent safety data to human risk assessment.

11.4 Pregnancy and developmental considerations

Elabela is essential for normal embryonic cardiovascular development [1, 9]. Exogenous administration during pregnancy is expected to activate APJ-dependent developmental programs and could theoretically influence fetal development. The preeclampsia model data suggest that ELA supplementation during pregnancy normalizes rather than disrupts fetal development in the setting of ELA deficiency [9], but the effect of supraphysiological ELA exposure on normal pregnancies has not been characterized.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five apelinergic system and related peptide candidates against Elabela, evaluated against five competency standards: novelty, effect size, promising potential (current research and translational state), side-effect profile (preclinical or clinical), and overall validation. The five candidates were selected as the principal ligands of the apelinergic system and related cardiovascular peptide systems with substantive preclinical or clinical pharmacology programs relevant to the therapeutic applications under investigation for Elabela.

12.1 Apelin-13 ([Pyr1]-apelin-13)

Mechanism: Endogenous peptide agonist of the apelin receptor (APJ/APLNR). Pyroglutamylated apelin-13 is the predominant circulating form of apelin in human plasma and the most extensively characterized isoform in pharmacological studies. Binding affinity at human APJ is in the low nanomolar range (K_i approximately 0.37 nM) [4, 37].

Development trajectory: Apelin was identified as the first endogenous APJ ligand in 1998 by Tatamoto et al. [24]. It has been studied extensively in cardiovascular physiology and disease for over 25 years, with a research literature exceeding 3,000 publications. A randomized, double-blind, placebo-controlled, crossover clinical trial of apelin infusion in chronic kidney disease patients was published by Mayeur et al. (2024), demonstrating cardiovascular and renal effects in humans [43].

Novelty: Low. Apelin is the canonical, longest-studied APJ agonist and the historical reference compound for the apelinergic system.

Effect size: In preclinical cardiovascular models, apelin-13 produces comparable positive inotropic, vasodilatory, and cardioprotective effects to Elabela. The Mayeur et al. (2024) human clinical trial demonstrated measurable cardiovascular and renal effects of acute apelin infusion in chronic kidney disease patients, providing the first direct human evidence of apelinergic system pharmacology [43].

Promising potential: Moderate. The clinical trial represents a major translational advance for the apelinergic system but highlights the limitation of the short in vivo half-life (approximately 5 minutes for apelin-13, shorter than ELA-32). Modified apelin analogs are in development.

Side-effect profile: In the human clinical trial, apelin infusion was well tolerated with no serious adverse events. The principal pharmacological effect (vasodilation) was the intended therapeutic effect. The short half-life limits both therapeutic utility and adverse-event duration.

Overall validation: High. Apelin-13 has the most extensive preclinical literature, the first completed human clinical trial in the apelinergic system, and the longest research history.

Comparison to Elabela: Apelin-13 and Elabela are co-ligands of the same receptor with complementary developmental and adult physiological roles. Elabela has the advantage of developmental non-redundancy (essential for cardiac morphogenesis and placental angiogenesis where apelin is dispensable), moderately longer plasma half-life, resistance to ACE2-mediated degradation, and the preeclampsia therapeutic rationale. Apelin-13 has the advantages of an established clinical-trial record, a larger research literature, and better-characterized pharmacology.

12.2 MM07 (cyclic apelin analog)

Mechanism: Metabolically stable cyclic peptide analog of apelin, designed to resist ACE2-mediated C-terminal cleavage while retaining apelin receptor agonist activity. MM07 is a macrocyclic analog that constrains the C-terminal pharmacophore of apelin into a proteolysis-resistant conformation [30, 44].

Development trajectory: Developed by Read et al. (2016) and subsequently characterized in human and rat cardiovascular studies. Phase 1 clinical studies have been conducted in healthy volunteers and heart failure patients in Edinburgh, demonstrating safety and hemodynamic activity [44].

Novelty: Moderate to high. The macrocyclic stabilization approach is a significant medicinal chemistry advance over native peptide ligands and represents a viable translational strategy for the apelinergic system.

Effect size: In healthy volunteer and heart failure patient studies, MM07 infusion produced dose-dependent increases in cardiac output and reductions in peripheral vascular resistance, with effect sizes comparable to or greater than those of native apelin infusion at equivalent doses [44].

Promising potential: Moderate to high. The compound has demonstrated clinical proof-of-concept for APJ agonism in heart failure and is in early-phase clinical development. It represents the most advanced translational candidate in the apelin-ergic system.

Side-effect profile: Well tolerated in Phase 1 clinical studies; no serious adverse events reported. Hemodynamic effects (vasodilation, increased cardiac output) are the intended pharmacological actions.

Overall validation: Moderate. Early clinical data support the translational viability of metabolically stable APJ agonists. The literature is smaller than that for native apelin.

Comparison to Elabela: MM07 represents the synthetic stabilization approach to the translational challenge shared by all apelinergic peptides. Elabela's advantages are its endogenous developmental and obstetric biology, its distinct signaling bias profile, and the non-redundant preeclampsia and stem cell biology that apelin analogs do not share. MM07's advantages are clinical development stage, metabolic stability, and the ability to administer as a simple peptide without Fc-fusion or PEGylation.

12.3 AMG-986 (small-molecule APJ agonist)

Mechanism: Non-peptide small-molecule agonist of the apelin receptor, developed by Amgen for the treatment of heart failure. AMG-986 was the first orally bioavailable APJ agonist to enter human clinical trials [45].

Development trajectory: AMG-986 completed a Phase 1 clinical trial in healthy volunteers (NCT03406507) demonstrating safety and pharmacokinetic characterization, followed by a Phase 2a proof-of-concept study in heart failure patients. Amgen subsequently discontinued development of AMG-986 and advanced a follow-on compound.

Novelty: High. As the first small-molecule, orally bioavailable APJ agonist to enter clinical development, AMG-986 represents a fundamentally different approach to apelinergic pharmacology than the peptide ligands.

Effect size: Phase 1 and Phase 2a data have not been fully published in peer-reviewed form as of the monograph revision date. Preclinical data in rodent heart failure models demonstrated dose-dependent improvements in cardiac function.

Promising potential: Moderate. Development of the specific compound AMG-986 has been deprioritized, but the small-molecule APJ agonist approach continues in Amgen's pipeline and at other companies. Oral bioavailability is the principal translational advantage over peptide ligands.

Side-effect profile: Phase 1 data indicate acceptable tolerability. Detailed adverse-event reporting has not been published in peer-reviewed form.

Overall validation: Low to moderate. The compound serves as proof-of-concept for the small-molecule APJ agonist approach but has not produced a registered medicine.

Comparison to Elabela: AMG-986 has the fundamental advantage of oral bioavailability, which no Elabela preparation achieves. Elabela has the advantages of endogenous biology, developmental essentiality, the preeclampsia and stem cell rationales, and the diversity of preclinical evidence across cardiovascular, renal, and neurological models. The two represent complementary approaches to APJ agonism: endogenous peptide biology versus synthetic medicinal chemistry.

12.4 Alamandine

Mechanism: Endogenous heptapeptide of the renin-angiotensin system (Ala-Arg-Val-Tyr-Ile-His-Pro), acting as an agonist of the Mas-related G-protein-coupled receptor D (MrgD). Alamandine is produced by decarboxylation of angiotensin-(1-7) or by ACE2-mediated cleavage of angiotensin A, and represents the counter-regulatory protective arm of the RAS in parallel to the apelinergic system [46].

Development trajectory: Identified by Lautner et al. (2013) as a novel component of the renin-angiotensin system with vasodilatory and cardioprotective properties. Preclinical studies have demonstrated anti-fibrotic, anti-hypertensive, and cardioprotective effects in rodent models, including attenuation of myocardial infarction-induced heart failure and fibrosis [46, 47].

Novelty: Moderate. The MrgD receptor axis is a relatively recently characterized component of the RAS. The peptide is mechanistically distinct from Elabela (different receptor, different signaling cascades) but shares overlapping cardiovascular protective endpoints.

Effect size: Moderate in rodent cardiac fibrosis and heart failure models. Effect sizes are broadly comparable to those reported for ELA in similar models, though direct head-to-head comparisons have not been performed.

Promising potential: Low to moderate. No human clinical trials have been completed. The compound remains in preclinical investigation.

Side-effect profile: Preclinical only. No material safety concerns in published animal studies.

Overall validation: Low to moderate. The preclinical literature is smaller than that for Elabela and substantially smaller than that for apelin. The MrgD receptor biology is less well characterized than APJ biology.

Comparison to Elabela: Alamandine and Elabela represent parallel endogenous counter-regulatory peptide systems (RAS-protective and apelinergic, respectively) that converge on overlapping cardiovascular protective endpoints. The two systems may be synergistic; combination studies have not been reported. Elabela has the advantages of a larger research literature, developmental essentiality, and more diverse preclinical applications (renal, obstetric, neurological, stem cell).

12.5 Relaxin-2 (serelaxin)

Mechanism: Endogenous peptide hormone of the relaxin/insulin superfamily acting on the relaxin family peptide receptor 1 (RXFP1), a leucine-rich repeat G-protein-coupled receptor. Relaxin-2 produces vasodilation, anti-fibrosis, anti-inflammation, and angiogenesis through nitric oxide-dependent and cAMP/PI3K/AKT-dependent signaling [48].

Development trajectory: Recombinant human relaxin-2 (serelaxin) was developed by Novartis for the treatment of acute heart failure. The RELAX-AHF Phase 3 trial (2013) in 1,161 acute heart failure patients demonstrated significant improvement in dyspnea and a reduction in 180-day cardiovascular mortality (a secondary endpoint) [49]. However, the confirmatory RELAX-AHF-2 Phase 3 trial (2019) in

6,545 patients failed to meet its co-primary endpoints of cardiovascular death at 180 days and worsening heart failure at 5 days, and Novartis discontinued the program [50].

Novelty: Moderate. The relaxin/RXFP1 axis is a well-characterized endogenous cardiovascular peptide system distinct from the apelinergic system.

Effect size: The RELAX-AHF trial showed a statistically significant but modest effect on dyspnea relief and a suggestive reduction in cardiovascular mortality. The larger RELAX-AHF-2 trial did not confirm these findings, indicating that the clinical effect size was insufficient for registration.

Promising potential: Low. Novartis has discontinued serelaxin development for acute heart failure. Academic research continues on relaxin-2 for other indications (fibrotic diseases, preeclampsia).

Side-effect profile: Serelaxin was well tolerated in both Phase 3 trials. The principal adverse event was hypotension (consistent with the vasodilatory mechanism), which was dose-dependent and clinically manageable.

Overall validation: Moderate to high in terms of clinical data volume (two large Phase 3 trials) but ultimately negative for the primary heart failure indication. The relaxin biology is extensively validated at the preclinical level.

Comparison to Elabela: Serelaxin represents a cautionary precedent for the translational development of endogenous cardiovascular peptides: strong preclinical biology and an initially positive Phase 3 trial were not confirmed in a larger replication study, resulting in program termination. Elabela shares multiple mechanistic parallels with relaxin-2 (vasodilation, anti-fibrosis, angiogenesis, obstetric biology) through a different receptor system. The serelaxin experience informs the translational expectations for Elabela: preclinical cardioprotective and anti-fibrotic activity does not guarantee clinical registration-quality efficacy in large heart failure trials. Elabela's advantages relative to serelaxin are the diversity of non-redundant biology (developmental, stem cell, renal, preeclampsia) and the availability of alternative therapeutic indications beyond acute heart failure if that indication proves insufficiently responsive.

12.6 Comparator summary

The five comparator compounds span the apelinergic system (apelin-13, MM07, AMG-986) and related cardiovascular peptide systems (alamandine, serelaxin) with overlapping therapeutic targets. **Apelin-13** is the canonical reference ligand with the first completed human clinical trial in the field. **MM07** represents the most advanced clinically tested metabolically stable APJ agonist. **AMG-986** demonstrated the feasibility of orally bioavailable small-molecule APJ agonism. **Alamandine** is a parallel counter-regulatory peptide operating through the MrgD receptor. **Serelaxin** provides a cautionary translational precedent of a strongly validated endogenous cardiovascular peptide that failed in confirmatory Phase 3.

Elabela occupies a unique position among these comparators: it is the only compound with non-redundant developmental essentiality (cardiac morphogenesis, gastrulation), the only compound with an established preeclampsia loss-of-function model in mammals, the only compound with demonstrated stem cell self-renewal activity, and the compound with the broadest diversity of preclinical therapeutic evidence spanning cardiovascular, renal, obstetric, neurological, and oncological domains. Its principal limitations relative to the comparators are the absence of any human clinical trial data, the short in vivo half-life requiring modified analogs for chronic administration, and the absence of oral bioavailability.

The translational trajectory for Elabela will be informed by the outcomes of the apelin and MM07 clinical programs in heart failure and by the continued development of metabolically stable ELA analogs. The preeclampsia indication, for which Elabela has the strongest non-redundant mechanistic rationale, may represent the most differentiated clinical development opportunity relative to the comparator landscape.

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