



## Review

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# Structure-guided development of G protein-biased apelin receptor agonists for cardiovascular disease

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**Abstract:** Apelin receptor (APLNR) is a crucial G protein-coupled receptor that plays a central role in cardiovascular homeostasis; therefore, it represents a promising therapeutic target for heart failure, myocardial infarction, cardiac hypertrophy, and pulmonary arterial hypertension. However, the activation of APLNR simultaneously engages inhibitory G protein ( $G_i$ )-mediated protective signaling and  $\beta$ -arrestin pathways that are associated with pathological cardiac remodeling, thereby imposing significant limitations and challenges for the therapeutic development of conventional balanced agonists. Recent advances in structural biology and pharmacology have provided valuable mechanistic insights into receptor activation and biased signaling. High-resolution cryo-electron microscopy (cryo-EM) structures revealed the conformational basis of signal bias, enabling the rational design of fully G protein-biased agonists that retain cardiovascular benefits while avoiding hypertrophic effects. This review summarizes recent progress in APLNR signaling mechanisms and biased ligand development, highlighting a number of emerging strategies for the precision pharmacological targeting of this receptor.

**Key words:** Apelin receptor (APLNR); G protein-coupled receptor; Biased signaling; Drug design

## 1 Introduction

G protein-coupled receptors (GPCRs), constituting the largest family of membrane receptors in the human genome, regulate a broad spectrum of physiological processes. Owing to their central role in signal transduction, GPCRs represent one of the most successful classes of drug targets, with more than one-third of approved medicines acting on this receptor family (Lorente et al., 2025). In the cardiovascular system, GPCR signaling plays a pivotal role in controlling myocardial contractility, vascular tone, fluid homeostasis, and cardiac remodeling. Unsurprisingly, dysregulation of these signaling pathways is closely associated with

the development of major cardiovascular diseases (Wang et al., 2018; Grogan et al., 2023). GPCRs have long been recognized as key therapeutic targets for treating cardiovascular conditions. Among them, the apelin receptor (APLNR), also known as APJ, has emerged as a highly promising target due to its direct protective actions on both the heart and vasculature (Chapman et al., 2023).

APLNR was initially classified as an orphan GPCR and was later found to be activated by the endogenous peptide ligand apelin and Elabela (ELA) (Tatemoto et al., 1998; Chng et al., 2013). The activation of APLNR by these peptides has been shown to exert a range of beneficial cardiovascular effects, including enhanced cardiac contractility, vasodilation, and protection against pathological remodeling (Kinjo et al., 2021; Rozwadowski et al., 2022; Gao and Chen, 2023). Despite these beneficial roles, the signaling properties of APLNR are intrinsically complex. Ligand binding can activate both inhibitory G protein ( $G_i$ )-mediated pathways and  $\beta$ -arrestin-dependent signaling. While  $G_i$  signaling is generally associated with cardioprotective effects, increasing evidence suggests that  $\beta$ -arrestin

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pathways may contribute to pathological cardiac remodeling under certain conditions (Scimia et al., 2012; Brame et al., 2015; Yang et al., 2019; Seo et al., 2020; Sun et al., 2025). This dual signaling property presents a major challenge for therapeutic development, as conventional balanced agonists may activate both beneficial and potentially detrimental pathways. Recent advances in structural biology, including studies from our group and others, have elucidated the conformational basis of APLNR activation and signaling bias (Yue et al., 2022, 2025b; Wang et al., 2024; Sun et al., 2025). These insights provide a foundation for the structure-guided design of biased agonists that selectively enhance cardioprotective signaling, representing an important step toward the precision pharmacological targeting of APLNR in cardiovascular disease.

## 2 Expression patterns and physiological roles of APLNR in the cardiovascular system

APLNR is broadly expressed in the cardiovascular system, such as in cardiomyocytes, vascular endothelial cells, vascular smooth muscle cells, and cardiac fibroblasts, where it contributes to the regulation of cardiac contractility, vascular tone, and cardiac remodeling (Kinjo et al., 2021; Rozwadowski et al., 2022). The activation of the apelin/APLNR signaling axis exerts multiple beneficial effects on cardiovascular physiology. In the heart, APLNR activation enhances myocardial contractility and improves cardiac performance without markedly increasing heart rate (Losano et al., 2005). In the vasculature, apelin signaling promotes vasodilation primarily through endothelial nitric oxide-dependent mechanisms, thereby reducing peripheral vascular resistance and contributing to blood pressure regulation (Zhong et al., 2007). In addition, the apelin/APLNR system participates in the control of fluid homeostasis by promoting natriuresis and diuresis (Chapman et al., 2024). Beyond these physiological functions, accumulating evidence indicates that APLNR activation exerts protective effects under pathological conditions. In experimental models of cardiovascular stress, stimulation of the apelin/APLNR pathway attenuated cardiac hypertrophy, suppressed fibrosis, and improved cardiac function, highlighting its therapeutic potential in heart failure and other cardiovascular diseases (Marczewski et al., 2022; Tang

et al., 2024; Girault-Sotias et al., 2025; Hasheminezhad et al., 2025).

Collectively, these findings establish the apelin/APLNR axis as an important endogenous regulatory system that integrates cardiac contractility, vascular tone, and fluid homeostasis. However, understanding how APLNR signaling produces these diverse physiological effects requires a detailed examination of the molecular mechanisms that govern receptor activation and downstream signaling.

## 3 Molecular regulatory mechanisms of APLNR signaling

### 3.1 Structural mechanism of APLNR activation

Structural studies over the past few years have significantly advanced our understanding of how APLNR is activated and how ligand recognition is translated into distinct downstream signaling outputs. The first major breakthrough came from the work of Yue et al. (2022), who resolved the cryo-electron microscopy (cryo-EM) structure of the APLNR homodimer in complex with the G<sub>i</sub> protein, providing the first structural evidence of a class A GPCR dimer bound to a G protein. Their study revealed that the receptor forms a symmetric homodimer mediated by a small hydrophobic interface located at the transmembrane helix 3–extracellular loop 1 (TM3–ECL1) region, involving the conserved FGTF motif. Importantly, within this dimeric assembly, only one protomer is directly coupled to the G<sub>i</sub> protein, while the second protomer remains uncoupled, suggesting an asymmetric mode of activation. This structural feature suggests that APLNR dimers do not signal through the simultaneous activation of both protomers; rather, signal transduction occurs via an asymmetric “two receptors–one G protein” coupling mechanism, thereby establishing a defined receptor–G protein stoichiometry.

Building upon this framework, our group further determined multiple structures of APLNR activated by distinct ligands, including endogenous peptide agonists and small-molecule agonists, thereby expanding the mechanistic understanding of receptor activation (Wang et al., 2024). Structural analyses of the endogenous ligand apelin, the G protein-biased peptide agonist MM07, and the small-molecule agonist CMF-019 revealed the presence of both shared and ligand-specific

mechanisms of receptor activation. In all cases, ligand engagement within the orthosteric pocket stabilized the outward displacement of TM6 and rearrangement of the conserved microswitch network, thereby creating a cytoplasmic interface competent for  $G_i$  coupling. However, these ligands exhibit distinct binding modes and conformational effects on the receptor. The endogenous peptide apelin inserts its C-terminal residues deep into the transmembrane core, establishing extensive polar and hydrophobic interactions that stabilize a canonical active conformation of APLNR. In contrast, MM07 adopts a modified peptide conformation that reinforces interactions with key residues in the upper transmembrane cavity and extracellular loops, preferentially stabilizing receptor conformations that favor  $G_i$  engagement while limiting  $\beta$ -arrestin recruitment. The small-molecule agonist CMF-019 occupies a more compact binding pocket within the transmembrane bundle and activates the receptor through a distinct set of interactions that converge on the same intracellular activation switches. Together, these structures reveal how chemically diverse ligands converge on a common activation pathway while stabilizing distinct conformational intermediates, providing a structural basis for ligand-dependent signaling bias and offering new insights into the rational design of selective APLNR modulators.

### 3.2 Molecular basis of biased signaling

The divergent physiological outcomes of  $G_i$ - and  $\beta$ -arrestin-mediated APLNR signaling have driven a strong interest in uncovering the structural determinants of signaling bias and in developing ligands that selectively engage beneficial pathways. Our studies first uncovered the molecular mechanism of biased signaling in APLNR. Cryo-EM structures of APLNR- $G_i$  complexes bound to distinct agonists revealed that ligand-dependent remodeling of the orthosteric pocket propagates through conserved microswitch networks to the intracellular surface, thereby controlling transducer coupling (Wang et al., 2024). These analyses further defined “twin hotspots”—the deep binding pockets accommodating the key residues M11 and F13 of apelin that serve as key structural elements determining receptor selectivity toward downstream signaling effectors. This mechanistic insight directly guided the rational design of two fully  $G_i$ -biased agonists, WN353 and WN561.

Beyond ligand binding, receptor oligomerization has emerged as a critical modulator of signaling bias. High-resolution cryo-EM structures of APLNR dimers across multiple conformational states ranging from apo, antagonist-bound, intermediate, to fully G protein-coupled active states have illuminated how dimer dynamics influence transducer selectivity (Yue et al., 2025a; Ji et al., 2026). These structures reveal that APLNR dimers preferentially couple to a single  $G_i$  heterotrimer, adopting a 2:1 receptor-G protein stoichiometry, whereas monomers engage  $G_i$  in a canonical 1:1 complex. Notably, our study highlighted that G protein binding induces steric clashes with the non-coupled protomer, facilitating dimer dissociation and promoting monomer formation during activation (Ji et al., 2026). Functional studies further demonstrated that monomeric APLNR exhibits significantly higher  $\beta$ -arrestin activity compared to the dimeric form, while  $G_i$  signaling remains comparable between the two states. This oligomerization-dependent bias indicates that dimeric APLNR inherently favors  $G_i$  signaling by limiting  $\beta$ -arrestin coupling, whereas monomers possess enhanced potential to engage arrestin pathways and may thus contribute to adverse hypertrophic signaling. Moreover, our findings showed that different ligands exhibit distinct propensities to induce dimer pre-dissociation in the intermediate G protein-free state: higher potency agonists such as AMG986 penetrate more deeply into the orthosteric pocket, inducing conformational changes that predispose the dimer to dissociate upon G protein binding and thereby promote  $\beta$ -arrestin-prone monomer formation (Ji et al., 2026). However, an important unresolved question remains: whether this oligomerization-dependent mechanism also contributes to the pharmacological profiles of relatively weak or  $G_i$ -biased agonists, including MM07, WN353, and WN561. At present, there is no direct evidence establishing how these ligands regulate the dimer-monomer equilibrium of APLNR; hence, it remains unknown whether their  $G_i$ -biased properties are associated with reduced dimer pre-dissociation and preferential stabilization of the dimeric receptor or are largely independent of the receptor oligomeric state. Resolving this question will require the direct characterization of ligand-dependent receptor oligomerization using complementary structural and quantitative approaches in living cells. Such studies will be particularly important for determining whether controlling the dimer-to-monomer transition

represents an additional, therapeutically exploitable dimension of APLNR signaling bias. This ligand-dependent modulation of oligomeric dynamics adds an additional layer of complexity to biased signaling, suggesting that optimal therapeutic profiles may require not only the selective stabilization of  $G_i$ -favoring conformations but also the modulation of receptor oligomeric states to minimize  $\beta$ -arrestin engagement.

Collectively, these structural and functional insights establish a multidimensional framework for understanding APLNR-biased signaling, thereby enabling the rational design of fully  $G_i$ -biased agonists with improved safety profiles and providing a paradigm for developing pathway-selective therapeutics targeting other GPCRs where biased signaling offers therapeutic advantages (Fig. 1).

#### 4 Precision pharmacological targeting of APLNR: development of biased agonists

The elucidation of the APLNR multidimensional biased signaling framework has provided a rational foundation for the development of next-generation therapeutics with enhanced safety profiles. At the same time, the evolution from balanced agonists to fully  $G$  protein-biased agonists has been fraught with challenges, primarily due to the difficulty of mitigating

$\beta$ -arrestin-mediated adverse effects such as cardiac hypertrophy. Over the past decade, several small-molecule agonists, including AMG986 (NCT03276728), BMS-986224 (NCT03281122), and CLR325 (NCT02696967), have advanced to clinical trials but have yet to demonstrate clear therapeutic advantages for heart failure, highlighting the critical need for more sophisticated design strategies.

Early efforts to achieve biased signaling yielded partially  $G$  protein-biased agonists, such as MM07 and CMF-019, which showed promise in preclinical studies by demonstrating reduced  $\beta$ -arrestin recruitment compared to apelin. However, these compounds exhibited diminished  $G$  protein activity relative to the endogenous ligand and retained residual  $\beta$ -arrestin engagement, limiting their therapeutic potential. Notably, functional characterization revealed that while CMF-019 preserved cardiomyocyte viability and mitochondrial function under pathological stress, it failed to abolish pro-hypertrophic effects and exhibited no anti-fibrotic activity, underscoring the limitations of partial bias (Read et al., 2021; Sun et al., 2025).

Based on two distinct structural mechanisms, the authors of this review and other researchers have successfully developed highly selective  $G$  protein-biased agonists. We obtained WN561, the first designed fully biased APLNR agonist, through structure-guided analysis and engineering of the “twin hotspot” regions

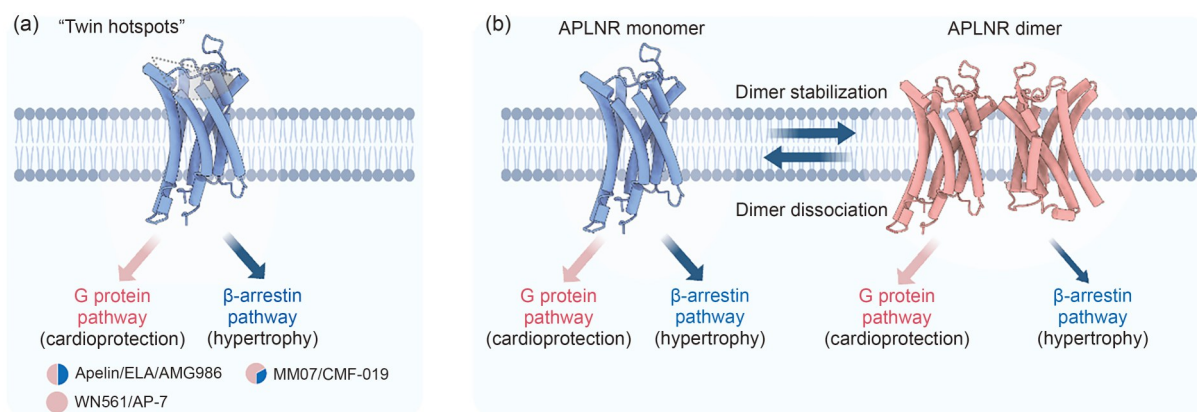


**Fig. 1** Model for the signaling bias regulation of apelin receptor (APLNR) monomers and dimers. The APLNR signaling bias is regulated by two complementary mechanisms: ligand-dependent conformational selection within the orthosteric binding pocket and receptor oligomerization. (a) The ligand-binding pocket contains “twin hotspots,” where different ligands adopt distinct binding poses that induce specific receptor conformations and thereby selectively modulate downstream signaling pathways. Balanced agonists (apelin/Elabela (ELA)/AMG986; pink denotes  $G$  protein and blue denotes  $\beta$ -arrestin; pie diagrams represent the proportional contributions of different signaling pathways) activate both  $G$  protein and  $\beta$ -arrestin pathways, whereas partially biased agonists (MM07/CMF-019) and fully  $G$  protein-biased agonists (WN561/AP-7) exhibit varying degrees of signaling bias. (b) The stabilization of dimeric receptor conformation favors the maintenance of  $G$  protein signaling while reducing  $\beta$ -arrestin recruitment.

of endogenous ligand–receptor interaction. Cryo-EM validation confirmed that WN561 stabilizes a receptor conformation that fully activates the  $G_i$  protein while precluding the rearrangements required for  $\beta$ -arrestin recruitment, thereby effectively counteracting cardiac hypertrophy and reducing side effects in preclinical models (Wang et al., 2024). Subsequently, AP-7 was developed by Sun et al. (2025) through a “biased chemical space remodeling” strategy leveraging the high-resolution structure of the CMF-019–APLNR– $G_i$  complex. This compound completely abolishes  $\beta$ -arrestin signaling by disrupting the Y264<sup>6.51</sup>–K268<sup>6.55</sup> electrostatic interaction network critical for  $\beta$ -arrestin recruitment, while it demonstrated superior therapeutic efficacy in heart failure with preserved ejection fraction (HFpEF) mouse models by improving glucose tolerance and attenuating cardiac hypertrophy and fibrosis. Together, these two cases demonstrate that design strategies based on detailed structural mechanisms can be successful in developing next-generation biased drugs with precise signaling profiles.

## 5 Future directions: AI-driven design and oligomer-selective targeting of APLNR agonists

The successful development of fully  $G_i$ -biased agonists WN561 and AP-7 demonstrates that structure-guided design can achieve precise modulation of APLNR signaling. Building upon these advances, emerging strategies integrating artificial intelligence (AI) and oligomer-selective targeting, including AI-accelerated peptide and small-molecule discovery, promise to further expand the therapeutic landscape. The expanding structural dataset of APLNR, which encompasses multiple conformational states, diverse ligand chemotypes, and both monomeric and dimeric assemblies, provides an ideal foundation for machine learning approaches. Deep learning architectures, including graph neural networks, transformers, and diffusion models, have revolutionized peptide design by enabling the generation of novel sequences with predefined binding properties (Rettie et al., 2025a; Scharbert and Strodel, 2025; Ekambaram and Dokholyan, 2026). AI-driven approaches offer particular advantages for peptide therapeutics: they can explore a vast chemical space beyond natural amino acids, integrate non-canonical amino acids to enhance metabolic stability, and predict key drug-like

parameters such as toxicity, solubility, and permeability, thereby reducing experimental screening costs (Choudhury et al., 2025).

Recent advances provide relevant precedents for applying these approaches to constrained ligands and GPCR modulators. Two complementary foundational methods illustrate the capabilities of AI-enabled protein engineering: ProteinMPNN designs amino acid sequences conditioned on a specified backbone (Dauparas et al., 2022), whereas RFdiffusion generates protein backbones that can be subsequently coupled to sequence design and experimental screening (Watson et al., 2023). In 2025, an adapted diffusion-based workflow enabled the design and experimental validation of high-affinity protein-binding macrocycles (Rettie et al., 2025b). This study extended generative protein design toward compact, conformationally constrained scaffolds and therefore provided a useful methodological precedent for peptide-like ligand discovery, although it did not establish APLNR binding or signaling bias.

The conceptual connection to GPCR pharmacology became more direct with the development of de novo-designed GPCR exoframe modulators. In 2026, certain designed membrane proteins were shown to engage the transmembrane surface of the dopamine D1 receptor and modulate receptor signaling allosterically (Cheng et al., 2026). This demonstrates that computationally designed molecules can regulate GPCR function by targeting receptor surfaces outside the conventional orthosteric pocket, thereby expanding the druggable landscape of GPCRs. However, whether this strategy can be translated to APLNR and, importantly, whether designed modulators can selectively target distinct APLNR conformational or oligomeric states remain unknown. APLNR-directed designs will therefore require the experimental confirmation of binding, receptor selectivity,  $G_i$  activation,  $\beta$ -arrestin recruitment, and oligomeric-state effects rather than relying on structural predictions alone.

Beyond molecular generation, advances in structural biology are beginning to provide the dynamic information needed to define which receptor states should be targeted. Time-resolved cryo-EM of the  $\beta_2$ -adrenergic receptor–stimulatory G protein ( $G_s$ ) complex could capture successive intermediates after guanosine triphosphate (GTP) addition, resolving conformational changes during G protein activation and dissociation (Papaserghi-Scott et al., 2024). Such temporal information

complements static endpoint structures and suggests that future APLNR ligand design could move from targeting a single structural snapshot toward targeting a conformational ensemble. However, the kinetics and intermediates observed for  $\beta$ 2-adrenergic receptor– $G_s$  cannot be assumed to apply directly to APLNR– $G_i$ . Combining time-resolved structural approaches with signaling and oligomerization measurements may therefore reveal transient APLNR states that are selectively associated with  $G_i$  versus  $\beta$ -arrestin signaling and thus provide new templates for state-selective ligand design.

These dynamically defined receptor states could then provide structurally informed templates for AI-guided molecular design, linking the characterization of APLNR conformational ensembles directly to the generation of state-selective ligands. In this framework, generative chemistry algorithms, trained on the structural determinants of bias identified in our studies (including the Y264<sup>6.51</sup>–K268<sup>6.55</sup> electrostatic network), can explore previously inaccessible chemical space to design novel scaffolds with predefined signaling profiles, accelerating the discovery of orally bioavailable candidates with optimized pharmacokinetics. Furthermore, the recognition that APLNR monomers and dimers exhibit distinct signaling propensities, whereby dimers inherently favor  $G_i$  signaling whereas monomers promote  $\beta$ -arrestin engagement, opens an unexplored dimension for therapeutic intervention. Ligands that stabilize the dimeric configuration or slow the G protein-induced dimer-to-monomer transition could provide therapeutic benefit for cardiovascular indications where minimizing  $\beta$ -arrestin activity is of paramount significance. The structural resolution of the dimer interface, particularly the cholesterol-stabilized intracellular contacts and the F101<sup>3.24</sup> “dimer switch,” yields precise molecular targets for developing allosteric modulators that bias receptor oligomeric equilibrium. Such approaches could complement traditional orthosteric bias, offering an additional layer of selectivity in fine-tuning therapeutic outcomes by targeting specific receptor quaternary structures.

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## Author contributions

Yan ZHANG conceptualized the review, established the overall structure of the manuscript, supervised the study, and

revised the manuscript critically for important intellectual content; Weiwei WANG performed the literature analysis, prepared the schematic figures, and wrote the initial draft; Jiangrong ZHANG, Jiahua ZHANG, and Yixin YANG assisted with literature collection and data interpretation. All authors contributed to manuscript revision and approved the final version.

## Compliance with ethics guidelines

Weiwei WANG, Jiangrong ZHANG, Jiahua ZHANG, Yixin YANG, and Yan ZHANG declare that they have no conflicts of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

## Declaration on the use of generative AI tools

No generative AI tools were used in the preparation of this manuscript.

## References

- Brame AL, Maguire JJ, Yang PR, et al., 2015. Design, characterization, and first-in-human study of the vascular actions of a novel biased apelin receptor agonist. *Hypertension*, 65(4):834-840.  
<https://doi.org/10.1161/hypertensionaha.114.05099>
- Chapman FA, Maguire JJ, Newby DE, et al., 2023. Targeting the apelin system for the treatment of cardiovascular diseases. *Cardiovasc Res*, 119(17):2683-2696.  
<https://doi.org/10.1093/cvr/cvad171>
- Chapman FA, Melville V, Godden E, et al., 2024. Cardiovascular and renal effects of apelin in chronic kidney disease: a randomised, double-blind, placebo-controlled, crossover study. *Nat Commun*, 15:8387.  
<https://doi.org/10.1038/s41467-024-52447-7>
- Cheng SZ, Guo J, Zhou YL, et al., 2026. De novo design of GPCR exoframe modulators. *Nature*, 651(8104):242-250.  
<https://doi.org/10.1038/s41586-025-09957-1>
- Chng SC, Ho L, Tian J, et al., 2013. ELABELA: a hormone essential for heart development signals via the apelin receptor. *Dev Cell*, 27(6):672-680.  
<https://doi.org/10.1016/j.devcel.2013.11.002>
- Choudhury PR, Mishra SK, Yadav S, et al., 2025. In silico peptide design: methods, resources, and role of AI. *J Pept Sci*, 31(12):e70063.  
<https://doi.org/10.1002/psc.70063>
- Dauparas J, Anishchenko I, Bennett N, et al., 2022. Robust deep learning-based protein sequence design using ProteinMPNN. *Science*, 378(6615):49-56.  
<https://doi.org/10.1126/science.add2187>
- Ekambaram S, Dokholyan NV, 2026. Peptide-based drug design using generative AI. *Chem Commun*, 62(3):672-691.  
<https://doi.org/10.1039/d5cc04998a>
- Gao SH, Chen HP, 2023. Therapeutic potential of apelin and Elabela in cardiovascular disease. *Biomed Pharmacother*, 166:115268.  
<https://doi.org/10.1016/j.biopha.2023.115268>
- Girault-Sotias PE, Deloux R, de Mota N, et al., 2025. The

- metabolically resistant apelin-17 analogue LIT01-196 reduces cardiac dysfunction and remodelling in heart failure after myocardial infarction. *Can J Cardiol*, 41(5):911-924. <https://doi.org/10.1016/j.cjca.2024.11.034>
- Grogan A, Lucero EY, Jiang HR, et al., 2023. Pathophysiology and pharmacology of G protein-coupled receptors in the heart. *Cardiovasc Res*, 119(5):1117-1129. <https://doi.org/10.1093/cvr/cvac171>
- Hasheminezhad MM, Mirzad M, Vafa SS, et al., 2025. Early administration of apelin could prevent heart failure following myocardial injury; a systematic review and meta-analysis. *Arch Acad Emerg Med*, 13(1):e4. <https://doi.org/10.22037/aaem.v13i1.2414>
- Ji SY, Wang WW, Yang YX, et al., 2026. Dynamic monomer-dimer transition in ligand-induced apelin receptor activation. *Nat Commun*, 17:4820. <https://doi.org/10.1038/s41467-026-71325-y>
- Kinjo T, Higashi H, Uno K, et al., 2021. Apelin/apelin receptor system: molecular characteristics, physiological roles, and prospects as a target for disease prevention and pharmacotherapy. *Curr Mol Pharmacol*, 14(2):210-219. <https://doi.org/10.2174/1874467213666200602133032>
- Lorente JS, Sokolov AV, Ferguson G, et al., 2025. GPCR drug discovery: new agents, targets and indications. *Nat Rev Drug Discov*, 24(6):458-479. <https://doi.org/10.1038/s41573-025-01139-y>
- Losano G, Penna C, Cappello S, et al., 2005. Activity of apelin and APJ receptors on myocardial contractility and vasomotor tone. *Ital Heart J Suppl*, 6(5):272-278.
- Marczewski K, Gospodarczyk N, Gospodarczyk A, et al., 2022. Apelin in heart failure. *Wiad Lek*, 75(10):2501-2506. <https://doi.org/10.36740/WLek202210130>
- Papasergi-Scott MM, Pérez-Hernández G, Batebi H, et al., 2024. Time-resolved cryo-EM of G-protein activation by a GPCR. *Nature*, 629(8014):1182-1191. <https://doi.org/10.1038/s41586-024-07153-1>
- Read C, Nyimanu D, Yang PR, et al., 2021. The G protein biased small molecule apelin agonist CMF-019 is disease modifying in endothelial cell apoptosis *in vitro* and induces vasodilatation without desensitisation *in vivo*. *Front Pharmacol*, 11:588669. <https://doi.org/10.3389/fphar.2020.588669>
- Rettie SA, Campbell KV, Bera AK, et al., 2025a. Cyclic peptide structure prediction and design using AlphaFold2. *Nat Commun*, 16:4730. <https://doi.org/10.1038/s41467-025-59940-7>
- Rettie SA, Juergens D, Adebomi V, et al., 2025b. Accurate de novo design of high-affinity protein-binding macrocycles using deep learning. *Nat Chem Biol*, 21(12):1948-1956. <https://doi.org/10.1038/s41589-025-01929-w>
- Rozwadowski J, Borodzicz-Jażdżyk S, Czarzasta K, et al., 2022. A review of the roles of apelin and ELABELA peptide ligands in cardiovascular disease, including heart failure and hypertension. *Med Sci Monit*, 28:e938112. <https://doi.org/10.12659/msm.938112>
- Scharbert L, Strodel B, 2025. Innovative strategies for modeling peptide-protein interactions and rational peptide drug design. *Curr Opin Struct Biol*, 93:103083. <https://doi.org/10.1016/j.sbi.2025.103083>
- Scimia MC, Hurtado C, Ray S, et al., 2012. APJ acts as a dual receptor in cardiac hypertrophy. *Nature*, 488(7411):394-398. <https://doi.org/10.1038/nature11263>
- Seo K, Parikh VN, Ashley EA, 2020. Stretch-induced biased signaling in angiotensin II type 1 and apelin receptors for the mediation of cardiac contractility and hypertrophy. *Front Physiol*, 11:181. <https://doi.org/10.3389/fphys.2020.00181>
- Sun Q, Tian XW, Tan L, et al., 2025. Multiscale biased chemical space remodeling for developing APLNR agonists with anti-HFpEF efficacy. *Proc Natl Acad Sci USA*, 122(18):e2423432122. <https://doi.org/10.1073/pnas.2423432122>
- Tang L, Qiu HL, Xu B, et al., 2024. Microparticle mediated delivery of apelin improves heart function in post myocardial infarction mice. *Circ Res*, 135(7):777-798. <https://doi.org/10.1161/circresaha.124.324608>
- Tatemoto K, Hosoya M, Habata Y, et al., 1998. Isolation and characterization of a novel endogenous peptide ligand for the human APJ receptor. *Biochem Biophys Res Commun*, 251(2):471-476. <https://doi.org/10.1006/bbrc.1998.9489>
- Wang JL, Gareri C, Rockman HA, 2018. G-protein-coupled receptors in heart disease. *Circ Res*, 123(6):716-735. <https://doi.org/10.1161/circresaha.118.311403>
- Wang WW, Ji SY, Zhang WJ, et al., 2024. Structure-based design of non-hypertrophic apelin receptor modulator. *Cell*, 187(6):1460-1475.e20. <https://doi.org/10.1016/j.cell.2024.02.004>
- Watson JL, Juergens D, Bennett NR, et al., 2023. De novo design of protein structure and function with RFdiffusion. *Nature*, 620(7976):1089-1100. <https://doi.org/10.1038/s41586-023-06415-8>
- Yang PR, Read C, Kuc RE, et al., 2019. A novel cyclic biased agonist of the apelin receptor, MM07, is disease modifying in the rat monocrotaline model of pulmonary arterial hypertension. *Br J Pharmacol*, 176(9):1206-1221. <https://doi.org/10.1111/bph.14603>
- Yue Y, Liu LE, Wu LJ, et al., 2022. Structural insight into apelin receptor-G protein stoichiometry. *Nat Struct Mol Biol*, 29(7):688-697. <https://doi.org/10.1038/s41594-022-00797-5>
- Yue Y, Liu LE, Wu LJ, et al., 2025a. Structural insights into the regulation of monomeric and dimeric apelin receptor. *Nat Commun*, 16:310. <https://doi.org/10.1038/s41467-024-55555-6>
- Yue Y, Xu CJ, Wu LJ, et al., 2025b. Mechanistic insights into the versatile stoichiometry and biased signaling of the apelin receptor-arrestin complex. *Nat Commun*, 16:7403. <https://doi.org/10.1038/s41467-025-62870-z>
- Zhong JC, Yu XY, Huang Y, et al., 2007. Apelin modulates aortic vascular tone via endothelial nitric oxide synthase phosphorylation pathway in diabetic mice. *Cardiovasc Res*, 74(3):388-395. <https://doi.org/10.1016/j.cardiores.2007.02.002>