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Nanocarrier-Enabled GPCR Therapeutics for Oncology, Neurological, and Cardiovascular Disorders

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Abstract

G protein–coupled receptors (GPCRs) constitute one of the largest and most pharmacologically significant classes of membrane proteins, regulating a broad spectrum of physiological processes and contributing to the pathogenesis of numerous diseases. Despite their central importance in therapeutic development, conventional GPCR-targeted drugs frequently encounter challenges such as poor solubility, inadequate bioavailability, rapid metabolic degradation, and off-target toxicity, which collectively limit their clinical effectiveness and therapeutic precision. This review aims to critically assess nanocarrier-based drug delivery approaches designed to enhance the targeting specificity, therapeutic efficacy, and translational potential of GPCR-modulating agents. A comprehensive analysis of peer-reviewed literature was conducted, focusing on GPCR structural biology, receptor signalling pathways, and advanced nanocarrier platforms, including liposomes, polymeric nanoparticles, dendrimers, and hybrid nanostructures. Emphasis was placed on preclinical investigations and early-phase clinical studies exploring GPCR-targeted nanomedicine strategies. Nanocarrier systems demonstrated significant improvements in pharmacokinetic and pharmacodynamic profiles by enabling controlled and sustained drug release, enhancing ligand stability, and facilitating targeted delivery to specific tissues. These systems also improved penetration across physiological barriers, including the blood–brain barrier, and supported the co-delivery of multiple therapeutic agents. Applications across oncology, neurological, and cardiovascular disorders highlight the broad therapeutic relevance of nanocarrier-assisted GPCR modulation. Nevertheless, challenges related to immunogenicity, long-term safety, large-scale manufacturing, and regulatory standardization remain critical considerations. Overall, nanocarrier-based delivery strategies offer a promising framework to overcome the limitations of conventional GPCR therapeutics and support the advancement of precision and personalized medicine.

Keywords: GPCRs, nanocarriers, drug delivery, liposomes, polymeric nanoparticles, precision medicine, targeted therapy

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1.Introduction

1.1 The centrality of GPCRs in human physiology

G protein–coupled receptors (GPCRs) are widely regarded as master regulators of intercellular communication and form the largest receptor family encoded within the human genome. GPCRs are distributed throughout virtually every organ system; GPCRs have evolved into highly versatile molecular switches that translate external cues into precise intracellular responses[1]. Unlike many receptor families that are limited to specific ligands or restricted physiological roles, GPCRs possess a breadth of recognition that spans an extraordinary spectrum of molecules and stimuli[2]**.** These include endocrine hormones that maintain systemic homeostasis, neurotransmitters that control the speed and tone of neuronal communication, lipid mediators that regulate inflammation and vascular dynamics, and sensory triggers such as photons and odorants that underlie vision and olfaction. This molecular diversity positions GPCRs as central hubs through which the body maintains both stability and responsiveness[3-4]**.**

Mechanistically, GPCRs exert their effects through dynamic interactions with heterotrimeric G proteins, which are classified into multiple subfamilies including Gs, Gi/o, Gq/11, and G12/13. Upon activation, these G proteins act as intracellular relays, stimulating downstream pathways such as cyclic AMP production, phospholipase activation, calcium mobilization, and Rho-family GTPase signaling[5-6]**.** These cascades ultimately alter gene transcription, protein activity, ion fluxes, and cytoskeletal architectural changes, which define how a cell behaves in real time and adapts over longer periods. Because of this multilayered control, GPCRs govern processes, such as heart rate modulation, vascular contraction, glucose metabolism, immune cell trafficking, synaptic plasticity, and sensory adaptation. It is not an exaggeration to state that GPCRs are indispensable for human survival in a collective system[7-8]**.**

This expansive functional role is mirrored by its dominance in pharmacology. GPCRs are the most targeted receptor family in modern medicine, accounting for a large fraction of the drugs currently in clinical use. Their modulation has produced therapeutic breakthroughs across disciplines: β-adrenergic receptor antagonists have revolutionized cardiovascular care, dopaminergic agents have reshaped psychiatric and neurological practice, and modulators of chemokine receptors have opened new avenues for cancer and infectious disease therapy[9]**.** This consistent track record of success highlights both the accessibility and drugability of GPCRs, cementing their reputation as the most fertile ground for therapeutic discovery[10]**.**

1.2 Limitations of conventional GPCR therapeutics

Despite their prominence, therapies designed to modulate GPCRs are far from flawless. Traditional approaches are largely based on small molecules or, more recently, peptide ligands,

which face multiple structural, pharmacological, and clinical challenges that limit their efficacy and safety. One of the most pressing concerns is lack of tissue selectivity[11]. Because GPCRs are often expressed in multiple organs simultaneously, a single drug acting systemically can rarely discriminate between beneficial and harmful sites of action. For example, an opioid targeting μ-opioid receptors may provide profound analgesia in the central nervous system; however, the same receptors in the gastrointestinal tract and respiratory centers can trigger constipation and potentially fatal respiratory depression. The problem of "on-target off-tissue" effects is pervasive across the GPCR landscape[12-14].

Another limitation is the phenomenon of receptor desensitization and tolerance. GPCRs are dynamic entities that are capable of internalization and downregulation when overexpressed. Chronic exposure to agonists often leads to diminished signaling via β-arrestin–mediated receptor internalization and degradation[15]. Clinically, this means that drugs that are initially effective may lose potency over time, forcing dose escalation and increasing the risk of adverse events. Such tolerance is particularly evident in therapies involving opioids, Î ²-agonists, or dopaminergic agents.[16]Peptide- and protein-based GPCR ligands present a different but equally problematic set of issues. Many of these ligands are inherently unstable in circulation as they are rapidly degraded by proteolytic enzymes. Even when intact, they typically exhibit poor oral bioavailability and short half-lives, requiring frequent injections or continuous infusion. This severely restricts patient compliance and overall therapeutic applicability[16]. Finally, structural similarity across the GPCR superfamily frequently leads to off-target interactions. Many ligands exhibit cross-reactivity with closely related receptors despite being rationally designed for specific receptor subtypes. This lack of precision can lead to severe and unexpected side effects. For example, serotonergic drugs often influence cardiac ion channels through unintended receptor interactions, occasionally leading to arrhythmias. Such cross-reactivity underscores the limitations of designing selective drugs in families characterized by conserved structural motifs[17-18].

1.3 Nanocarrier-based solutions: a paradigm shift

The advent of nanotechnology has led to a paradigm shift to address the shortcomings of conventional GPCR therapeutics. Nanocarriers, including liposomes, polymeric nanoparticles, dendrimers, micelles, and increasingly sophisticated biomimetic systems, provide platforms that can be engineered with extraordinary precision to optimize drug delivery[19]. One of their greatest advantages is the protection provided by fragile therapeutic agents. Encapsulation of peptide or protein ligands within nanocarriers shields them from enzymatic degradation, extending their stability and half-life in the circulation[20]. This directly addresses the major barriers faced by the biological GPCR ligands. Beyond stability, nanocarriers also enable the controlled and sustained release of drugs over extended periods rather than causing sharp systemic peaks. This pharmacokinetic smoothing reduces toxicity and improves therapeutic windows. Targeting ability represents another transformative feature[21]. Nanocarriers can be functionalized with tissue-specific

ligands, antibodies, or peptides, thereby concentrating the therapeutic payload at sites where specific GPCRs are overexpressed. For neurological diseases, nanocarriers modified with transferrin, lactoferrin, or cell-penetrating peptides can cross the blood–brain barrier, enabling drugs to reach dopaminergic or serotonergic receptors deep within the brain something conventional formulations struggle to achieve[22]. In oncology, nanoparticles decorated with chemokine receptor ligands can selectively accumulate in tumors, sparing healthy tissues and amplifying efficacy[23]. Beyond single-agent delivery, nanocarriers also provide platforms for combination therapies. They can simultaneously carry GPCR-targeting ligands, genetic modulators such as siRNA or miRNA, and imaging agents.[24]This convergence opens the door to theranostics integrated strategies where diagnosis and therapy occur in a seamless cycle, guided by the same nanoplatform; thus, nanocarriers do not simply refine GPCR pharmacology; they expand it, creating opportunities for precision targeting, barrier penetration, dual-function delivery, and patient-tailored therapies that were previously unimaginable with conventional drug design.

2. Methodology

This review was performed using a structured literature search strategy to identify studies on nanocarrier-based drug delivery systems specifically targeting G protein coupled receptors (GPCRs). Relevant articles published between 2020 and August 29, 2022, were retrieved from PubMed, Scopus, Web of Science, and Google Scholar using keywords including GPCRs, nanocarriers, drug delivery, liposomes, polymeric nanoparticles, dendrimers, targeted therapy, blood–brain barrier, and clinical translation. Peer-reviewed research articles, review papers, and clinical trial reports written in English that demonstrated preclinical or clinical relevance to oncology, neurology, cardiovascular disorders, or metabolic diseases were included, while studies not involving nanotechnology-based GPCR modulation, duplicated entries, and inaccessible full texts were excluded. An initial search yielded 256 results, of which 148 were selected following title and abstract screening, and 102 publications that met all the eligibility criteria were finally included in this synthesis. Data extraction focused on nanocarrier composition and design, GPCR signaling modulation mechanisms, pharmacokinetic and targeting advantages, therapeutic outcomes, toxicity and immunogenicity concerns, and translational barriers, such as regulatory and manufacturing issues. A narrative synthesis approach was employed to identify emerging trends, compare nanocarrier platforms, highlight innovations in artificial intelligence and personalized medicine integration, and map current progress to future opportunities for advancing GPCR-targeted nanomedicine[28].

3. GPCRs: Structure, Function, and Clinical Relevance

3.1 Structural insights into GPCR signaling

G protein–coupled receptors (GPCRs), often referred to as seven-transmembrane receptors, are the most abundant and structurally conserved class of human membrane proteins. The defining architectural hallmark is a heptahelical topology composed of seven α-helical transmembrane segments (TM1–TM7) that traverse the lipid bilayer in a serpentine manner.[29] These helices cluster to form a central ligand-binding cavity that can accommodate a diverse array of molecules ranging from small amines to large peptides and lipids[30]. The extracellular regions of GPCRs, including the N-terminus and connecting loops, often carry glycosylation sites that stabilize the receptor and play important roles in ligand recognition and selectivity. On the intracellular side, loops and the C-terminal tail act as docking platforms for heterotrimeric G proteins, G protein–coupled receptor kinases (GRKs), and β-arrestins, thereby orchestrating downstream signaling events[31].

When an agonist binds to a receptor, it induces conformational rearrangement within the transmembrane helices. This structural change propagates to the intracellular surface, where the receptor promotes the exchange of GDP for GTP on the α-subunit of the associated G protein. Activated Gα, along with liberated Gβγ dimers, engages downstream effectors to trigger various signaling pathways. Gs-coupled receptors stimulate adenylyl cyclases to elevate cyclic AMP levels, whereas Gi/o-coupled receptors inhibit adenylyl cyclase activity and reduce cAMP levels. Gq/11-coupled receptors activate phospholipase Cβ, producing IP3 and DAG, which mobilize calcium and activate protein kinase C. G12/13-coupled receptors influence the Rho-family GTPases to modulate cytoskeletal dynamics[32-33].

Importantly, GPCR signaling extends beyond these canonical G-protein pathways. β-arrestins, originally characterized as terminators of signaling that promotes receptor desensitization and internalization, are now recognized as scaffolds that initiate distinct G protein–independent pathways.[34]This dual signaling potential underlies the phenomenon of biased agonism, where certain ligands preferentially engage one pathway over another. Breakthroughs in structural biology, particularly X-ray crystallography and cryo-electron microscopy, have illuminated the atomic details of GPCR activation, allosteric modulation, oligomerization, and biased signaling. These insights have revolutionized drug design, offering the ability to engineer ligands that can fine-tune receptor responses with unprecedented precision[35].

3.2 Functional diversity of GPCRs

The functional diversity of GPCRs arises from their ubiquitous distribution across tissues and their signaling plasticity. In the nervous system, they control processes fundamental to mood, memory, and nociception. Dopamine receptors regulate motivation and reward circuits, serotonin receptors govern mood and cognition, and opioid receptors are central to pain modulation[36]. Within the

cardiovascular system, β-adrenergic receptors regulate heart rate and contractility, whereas angiotensin receptors influence vascular tone and blood pressure. The immune system relies heavily on chemokine receptors, such as CXCR4 and CCR5, which guide leukocyte migration and inflammatory responses[37]. Endocrine and metabolic regulation are equally dependent on GPCRs, with glucagon, GLP-1, and thyroid-stimulating hormone receptors acting as critical checkpoints for glucose balance, appetite control, and thyroid function. Finally, sensory perception is dominated by GPCR-mediated signaling, as exemplified by rhodopsin in vision and olfactory receptors in smell[38].

This versatility is amplified by the ability of GPCRs to engage in multiple signaling pathways, depending on the cellular context. A single receptor can couple to more than one G protein family, allowing context-dependent physiological outcomes. Biased signaling further adds to this complexity, enabling different ligands on the same receptor to preferentially trigger either G protein- or β-arrestin–mediated pathways[39]. Additionally, GPCRs do not function solely as isolated monomers; many exist as homo- or heterodimers and even higher-order oligomers, which confer unique signaling profiles distinct from their individual components. This layered complexity is both a therapeutic opportunity because it permits selective modulation of signaling axes and is challenging because it makes achieving drug specificity significantly more difficult[40].

3.3 GPCRs as therapeutic targets

The clinical relevance of GPCRs has been underscored by their dominance in drug development. A striking proportion of all approved medicines modulates GPCR function, reflecting both their accessibility to the cell surface and their central role in disease biology. β-adrenergic antagonists or β-blockers remain the cornerstone in the treatment of hypertension, arrhythmias, and heart failure[41]·Despite the side-effect burden of opioid receptor ligands, they continue to be indispensable for managing acute and chronic pain. Serotonin receptor modulators, ranging from selective serotonin reuptake enhancers to triptans, are widely used for psychiatric disorders and migraine therapy. In infectious diseases, CCR5 antagonists such as maraviroc provide life-saving options for HIV patients[42].

However, the therapeutic dominance of GPCRs has not yet eliminated these challenges. Poor subtype selectivity remains a recurring issue that often leads to dose-limiting toxicity and off-target side effects. The development of tolerance and desensitization with chronic use diminishes the long-term effectiveness of many GPCR-targeted drugs, forcing dose escalation and compounding adverse outcomes[43]. In some cases, systemic exposure results in the widespread activation or inhibition of receptors far beyond the intended tissue, thereby undermining safety. Another untapped frontier lies in approximately 120 “orphan receptors” for which endogenous ligands and their physiological roles remain poorly characterized. These receptors represent an enormous

reservoir of therapeutic opportunities but have been difficult to access using traditional pharmacology[44].

3.4 Rationale for nanocarrier-based GPCR therapies

The combination of GPCR pharmacology and nanotechnology provides a unique opportunity for overcoming these challenges. Nanocarriers such as liposomes, polymeric nanoparticles, dendrimers, micelles, and biomimetic platforms can be engineered to optimize drug delivery in ways that are unattainable by conventional formulations[45]. Encapsulation within nanocarriers stabilizes fragile peptides or protein ligands, protecting them from enzymatic degradation and prolonging their half-life in the circulation. This directly addresses the major limitations of biological GPCR ligands, many of which fail in clinical development due to instability[46].

Nanocarriers also offer the ability to fine-tune pharmacokinetics through controlled release, ensuring sustained therapeutic levels without sharp systemic peaks that can trigger toxicity. Surface modification allows for precise targeting. (Table 1) By conjugating antibodies, aptamers, or small receptor-specific ligands, nanoparticles can be directed toward tissues enriched in particular GPCRs, minimizing off-target activation.[47] Advanced nanocarriers can even traverse biological barriers such as the blood–brain barrier, which is critical for neurological applications such as the delivery of dopamine receptor ligands in Parkinson's disease or serotonin modulators in mood disorders, and the potential to exploit biased signaling and allosteric modulation through nanocarrier design. (Figure 2) By encapsulating biased agonists or allosteric ligands and delivering them in controlled-release formats, it is possible to sculpt receptor signaling in a highly selective manner.[48] Furthermore, nanoplatforms have created new possibilities for exploring orphan receptors. Stabilized delivery of candidate ligands in vivo could accelerate the discovery of receptor function and drugability, expanding the therapeutic reach of GPCR biology[49].

4.Nanocarrier Systems in GPCR-Targeted Therapy

Nanotechnology has revolutionized drug delivery by addressing the many limitations of conventional GPCR-targeted therapeutics, such as their rapid clearance, enzymatic degradation, poor solubility, and off-target side effects. Because GPCRs are widely expressed in multiple tissues, achieving selectivity is a major challenge. Nanocarrier-based systems offer solutions by shielding drugs from premature degradation, extending their circulation, and enabling targeted delivery to specific tissues and receptor subtypes[51]. Over the past two decades, several nanocarrier platforms, including liposomes, polymeric nanoparticles, dendrimers, and biomimetic carriers, have been explored in diverse therapeutic areas ranging from oncology and neurology to cardiovascular and immune disorders[52].

Liposomes remain the most clinically validated nanocarriers because of their biocompatibility and their ability to encapsulate both hydrophilic and hydrophobic GPCR ligands. PEGylation and ligand functionalization have further improved the circulation and receptor selectivity, with applications in anti-inflammatory therapy and neurological drug delivery. However, challenges such as stability, premature leakage, and high cost continue to limit their large-scale use.[53] Polymeric nanoparticles fabricated from biodegradable polymers, such as PLGA or chitosan, offer the advantages of controlled and sustained release, high drug-loading capacity, and dual delivery potential, particularly when co-formulated with siRNAs for GPCR gene modulation. Despite their promising applications in cancer and neuroendocrine diseases, issues of scale-up, reproducibility, and polymer-related toxicity remain barriers to their clinical translation[54].

Dendrimers provide unmatched structural precision and multivalency, enabling strong GPCR engagement through multiple ligand attachments while also serving as carriers for nucleic acids. Examples include PAMAM dendrimers conjugated with opioid peptides for enhanced analgesia, and dendrimer–siRNA complexes targeting CXCR4 in cancer. However, their high charge-associated toxicity, immune activation, and costly synthesis pose significant hurdles for their widespread adoption.[55]Biomimetic carriers, the newest entrants, exploit naturally derived materials such as cell membranes and exosomes to achieve immune evasion and tissue-specific targeting. These systems can extend the half-life of GPCR antagonists and cross biological barriers such as the blood–brain barrier, making them particularly attractive for neurological and oncological applications. Nonetheless, variability, scalability, and regulatory uncertainty continue to pose challenges to clinical advancements[56].

From a comparative perspective, each nanocarrier system offers distinct advantages, based on the therapeutic context.Liposomes are clinically proven but face stability issues: polymeric nanoparticles provide controlled release yet struggle with scale-up; dendrimers offer precision but risk cytotoxicity; and biomimetic systems promise immune stealth but lack manufacturing standardization[57]. No single platform was universally superior. Rational design based on disease pathology, receptor subtype distribution, and pharmacokinetic requirements, along with hybrid or next-generation strategies, may provide the most effective solutions for GPCR-targeted therapy[58].

5.Strategies for GPCR-Specific Targeting

The therapeutic success of nanocarrier-based GPCR modulation depends not only on the encapsulation of bioactive molecules but also on the ability to achieve receptor-specific delivery. GPCRs are expressed in virtually every tissue, and many subtypes share high structural homology.[59] Without precision targeting, systemic delivery can result in widespread off-target effects, toxicity, and diminished therapeutic benefits. To overcome these barriers, researchers have developed strategies that combine molecular recognition with nanotechnology to ensure high-fidelity engagement with the intended receptor population.[60] Broadly, these approaches can be

categorized into ligand functionalization, receptor-mediated uptake, stimuli-responsive nanocarriers, and integrative hybrid systems. Each strategy has unique strengths and limitations, and, in practice, their combination often provides the most clinically viable outcome.[61]

3.5 In Vivo Evaluation: Animal Models

Animal models serve as an indispensable bridge between cell-based assays and human trials. They provide insights into biodistribution, pharmacokinetics (PK), and therapeutic efficacy in the context of whole-organism physiological factors that in vitro systems cannot replicate. In oncology, polymeric nanoparticles functionalized with CXCR4 ligands have shown preferential accumulation in metastatic niches, suppressing tumor growth in xenograft-bearing mice. These findings underscore the potential of targeting chemokine receptors, which often drive tumor invasion and metastasis[62]. Neurological applications have gained immense momentum. For instance, transferrin-modified liposomes carrying dopaminergic agonists successfully crossed the blood–brain barrier in rodent models of Parkinson's disease and restored motor activity. This achievement represents a major breakthrough, given the historical difficulty of delivering drugs into the central nervous system, which presents a different challenge, where systemic delivery often causes undesirable hypotension[63]. AT1 receptor–targeted liposomes, however, have demonstrated enhanced selectivity for vascular smooth muscle cells in hypertensive rats, effectively lowering blood pressure without systemic side effects observed with free drugs. In pain management, PAMAM dendrimers functionalized with opioid peptides have shown superior penetration of the blood–brain barrier and prolonged analgesia in chronic pain models. Similarly, in inflammatory diseases, chemokine receptor–targeted biomimetic nanoparticles accumulate in inflamed tissues, improving the outcomes in rodent models of autoimmune arthritis.[64] Taken together, these in vivo studies consistently revealed a unifying theme: GPCR-targeted nanocarriers outperformed conventional formulations by enhancing efficacy while reducing off-target toxicity.

3.6 Early Clinical Translation

Although the field remains in its infancy, a handful of first-in-human applications signal the beginning of a paradigm shift. In oncology, CXCR4-targeted LNPs have entered early phase clinical trials (e.g., NCT04143850). Detailed clinical characteristics, including patient cohort size and reported response trends for key trials, are summarized in Supplementary Table S1 to enhance translational clarity. Preliminary data suggest favorable safety, tolerability, and predictable pharmacokinetics as key hurdles in nanoparticle translation, and neurology is moving toward clinical testing[65]. Liposomal formulations of dopaminergic agents are advancing as potential therapies for Parkinson's disease, designed specifically to enhance blood–brain barrier penetration and thereby overcome one of the field's most stubborn challenges. In inflammatory and autoimmune disorders, chemokine receptor–targeted nanocarriers remain in advanced preclinical pipelines, but several groups anticipate first-in-human studies in the near future. Finally,

theragnostic approaches that co-load therapeutic GPCR ligands with imaging probes have entered translational studies[66]. These platforms can accelerate both regulatory approval and personalized treatment planning by enabling the real-time visualization of receptor engagement and drug biodistribution.While no GPCR-targeted nanocarriers have yet achieved FDA or EMA approval, these first-wave trials represent a tangible step toward replacing systemic GPCR drugs with precision delivery platforms[67].

4. Discussion

The exploration of nanocarrier-based drug delivery systems targeting GPCRs represents a transformative approach in precision medicine. The findings presented throughout this chapter underscore the immense therapeutic potential of coupling nanotechnology with GPCR biology, particularly in overcoming traditional pharmacological barriers such as poor solubility, limited bioavailability, and off-target effects.One of the central themes emerging from the review is the dual advantage offered by nanocarriers: they not only improve the pharmacokinetic properties of GPCR-targeting agents but also enable spatiotemporal control over drug release. This is especially relevant for diseases in which GPCR signaling plays a central role in cancer, neurological disorders, and cardiovascular diseases[68]. The ability of nanocarriers to cross the blood–brain barrier or accumulate selectively in tumor tissues highlights their role as precision tools rather than simple drug vehicles[69]. However, the complexity inherent in GPCR-targeted nanomedicine must also be acknowledged. The heterogeneity of GPCR subtypes, coupled with variability in receptor conformation and tissue-specific expression, creates significant challenges for designing universally effective formulations[70]. Furthermore, despite encouraging preclinical results, the translation to clinical success remains limited. The gap between laboratory innovation and real-world applications is largely due to regulatory challenges, safety concerns, and the high cost of production and scale-up[71]. Another notable aspect is the role of nanocarriers in promoting combination therapies. Co-delivery of GPCR agonists or antagonists with other therapeutic agents (e.g., chemotherapeutics, siRNA, or peptides) opens new avenues for synergistic treatment strategies[72]. This not only enhances therapeutic efficacy but also provides a framework for addressing multidrug resistance, a major limitation in conventional treatments. Importantly, the integration of advanced nanocarrier systems with emerging tools such as artificial intelligence, molecular docking, and personalized medicine approaches is expected to reshape the landscape[73]. AI-driven modeling can assist in optimizing nanocarrier design, predicting pharmacokinetics, and tailoring therapies to patient-specific receptor profiles. This convergence of disciplines positions GPCR-targeted nanomedicine as the cornerstone for the next generation of precision therapeutics. In summary, while nanocarrier-based drug delivery systems targeting GPCRs hold considerable promise, their clinical translation requires balanced consideration of innovation, safety, scalability, and regulatory compliance. Bridging this gap is critical for shifting from conceptual frameworks

to tangible therapies that can significantly improve patient outcomes. The primary obstacle to clinical translation is not limited to nanocarrier engineering but is largely due to the biological heterogeneity of GPCR expression and signalling among patients. Even highly optimized nanocarriers are unlikely to achieve consistent clinical efficacy in the absence of comprehensive receptor profiling and stratified clinical trial designs[74].

7. Conclusion

Nanocarrier-drug delivery systems targeting GPCRs represent a worthy frontier in precision medicine developed with novel strategies to overcome the limitations associated with conventional therapeutics. Nanocarriers could reformulate GPCR-targeted therapies across fields, including oncology, neurology, cardiovascular disorders and many others by improving drug solubility (especially for small compounds), stability and bioavailability together with tissue- or cell typespecific delivery.

However, there are many hurdles remain for translating preclinical success into clinical application. Clinical translation of nanocarrier-based GPCR therapeutics continues to be delayed by multiple challenges spanning safety, immunogenicity, scalability, and regulatory approval hurdles. More nuanced approaches will need to combine nanotechnology with structural biology, computational modeling, and personalized medicine paradigms to overcome these hurdles. In the future, integrating nanomedicine with AI, omics technologies and personalized medicine strategies may unveil new horizons for targeted GPCR-based treatments: improved precision, effectiveness and safety. Despite several challenges, the way ahead is clear; continued innovation and robust validation paired with synergy between academia, industry and regulatory organizations will be critical to realizing the therapeutic potential of this field as it continues to evolve. Our expression of the nanocarrier-based GPCR-targeted drug delivery concept serves not only as a technological advancement in science, but also on a conceptual level, marks a paradigm shift in treatment design for precision medicine. Ongoing improvements can meaningfully enhance clinical outcomes and change treatment paradigms in a number of disease areas.

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