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Review

Nanocage-tethered Polymeric Hybridome for pDNA Delivery: A Revolutionary Approach for Treatment of Glioblastoma

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Abstract

Glioblastoma, a highly aggressive form of brain cancer, poses a formidable challenge in the field of oncology due to its resistance to conventional therapies and limited drug delivery options. This abstract highlights a groundbreaking strategy for combating glioblastoma by introducing a novel nanocage-tethered polymeric hybridome for the efficient and targeted delivery of plasmid DNA (pDNA). Our innovative approach combines the benefits of nanotechnology and polymer science to create a hybrid system capable of overcoming the inherent obstacles faced in glioblastoma treatment. The nanocage, acting as a carrier, not only ensures the protection and stability of the pDNA payload but also offers precise targeting capabilities. The tethering of polymers to the nanocage further enhances the biocompatibility, cellular uptake, and controlled release of pDNA. This nanocage-tethered polymeric hybridome has demonstrated exceptional potential in preclinical studies. It exhibits an unprecedented ability to penetrate the blood-brain barrier, specifically target glioblastoma cells, and efficiently deliver therapeutic pDNA payloads. Moreover, this approach minimizes off-target effects and reduces systemic toxicity, thus enhancing the safety profile. In conclusion, the development of the nanocage-tethered polymeric hybridome represents a paradigm shift in glioblastoma therapy.

1. Introduction

Glioblastoma, an aggressive and highly malignant brain tumor, continues to pose significant challenges in the field of oncology. Despite advances in our understanding of the disease and the development of various therapeutic strategies, the prognosis for glioblastoma patients remains grim [1]. The unique anatomical and physiological characteristics of the brain, coupled with the highly invasive nature of glioblastoma, render traditional treatment modalities largely ineffective. Consequently, there is an urgent need for innovative approaches that can offer more precise and potent therapies for this devastating disease [2]. In recent years, the field of nanomedicine has shown tremendous promise as a platform for delivering therapeutic payloads to specific target sites, thereby circumventing many of the limitations associated with conventional treatments. Among the diverse nanocarriers explored for drug delivery, nanocages have emerged as a particularly intriguing and versatile option [3]. These nanoscale structures offer a protective environment for therapeutic cargo while permitting precise control over release kinetics and targeting [4]. In the context of glioblastoma treatment, nanocages can serve as ideal carriers for delivering plasmid DNA (pDNA) encoding therapeutic genes, allowing for a more sustained and localized therapeutic effect [4,5].

Polymeric hybridomes, on the other hand, represent a cutting-edge approach that combines the unique advantages of nanocages with the versatility of polymers. By tethering nanocages with specially designed polymers, a hybrid delivery system can be engineered to maximize the stability, biocompatibility, and cellular uptake of pDNA [6]. This hybridome concept presents a revolutionary paradigm shift in the treatment of glioblastoma, offering the potential to overcome many of the obstacles that have hindered effective gene therapy in the past. In this commentary article, we will delve into the groundbreaking advancements in the development of nanocage-tethered polymeric hybridomes for pDNA delivery in the context of glioblastoma treatment [6,7]. We will discuss the rational design principles behind these hybrid systems, their unique attributes, and the promising results obtained in preclinical and early clinical studies. Furthermore, we will explore the multifaceted strategies employed to enhance the selectivity and specificity of pDNA delivery to glioblastoma cells while minimizing off-target effects. Finally, we will address the challenges and future prospects of this innovative approach, highlighting the potential it holds for revolutionizing the therapeutic landscape of glioblastoma and offering hope to patients and clinicians alike.

2. Glioblastoma Multiforme (GBM) and Its Treatment Challenges

Glioblastoma multiforme (GBM) remains one of the most aggressive and challenging brain cancers to treat, primarily due to its invasive growth pattern. Unlike other tumors that might form a distinct mass, GBM sends out tentacle-like projections deep into the surrounding brain tissue [8]. This makes surgical interventions exceedingly complex, as ensuring complete removal is near impossible. Compounding this surgical challenge is the body's natural defense mechanism - the blood-brain barrier (BBB) [9]. Designed to keep harmful substances out of the brain, the BBB inadvertently restricts many potential therapeutic agents from reaching the tumor, rendering systemic treatments less effective. Even when drugs manage to cross this barrier, the heterogeneous nature of GBM tumors presents another hurdle [10]. With a mix of different cell types within a single tumor, some cells may be inherently resistant to treatments, surviving initial interventions and potentially leading to recurrence. Currently available therapeutic options, although continuously evolving, are still limited [11]. The mainstay treatment, combining surgery with radiation and chemotherapy, often has to combat the rapid progression of the tumor. By the time many patients receive a GBM diagnosis, the tumor has frequently reached an advanced stage, thereby narrowing the window of effective intervention. Treatments, while aiming to be aggressive against the tumor, can inadvertently harm healthy brain tissue, leading to side effects such as cognitive decline and fatigue [12]. Furthermore, the propensity for GBM recurrence means that even after an initially successful treatment, patients are not out of danger. The recurrent tumors often exhibit heightened aggression and increased resistance to previously effective treatments [13]. This complex interplay of challenges underscores the urgent need for innovative therapeutic strategies and a deeper understanding of GBM's molecular intricacies. The potential of DNA as a therapeutic modality is vast, anchored in its ability to directly modulate cellular function and fate. Plasmid DNA (pDNA), small, circular, double-stranded DNA molecules that are distinct from chromosomal DNA, have emerged as powerful tools in the realm of gene therapy [14]. Unlike the permanent nature of chromosomal DNA, plasmids exist and replicate independently, making them ideal candidates for introducing transient genetic information into cells.

The therapeutic implications of pDNA are manifold. For diseases like glioblastoma multiforme (GBM), pDNA can be engineered to either introduce tumor-suppressing genes, enhance the expression of beneficial proteins, or inhibit the proliferation of malignant cells [15]. The strategy can also be geared towards promoting apoptosis, the natural process of programmed cell death, specifically in cancerous cells, or making the tumor more susceptible to conventional therapies such as radiation or chemotherapy [16]. However, the journey of pDNA from its point of introduction into the body to its target cells is fraught with challenges. The external milieu of the body, teeming with nucleases, poses a threat to the integrity of the pDNA. Moreover, the sheer size and negative charge of pDNA molecules impede their direct uptake by cells, necessitating the development of effective delivery vehicles like the aforementioned polymeric hybridomes. Safety is also paramount [17]. As with any gene therapy approach, the unintended integration of pDNA into the host's genome could lead to unforeseen consequences, including the potential activation of oncogenes. It's thus crucial that pDNA therapies be designed with precision, ensuring targeted action while minimizing off-target effects.

3. Nanocage Systems in Biomedical Applications

Nanocage systems, characterized by their highly organized and porous architectures, have emerged as versatile tools in biomedical applications due to their unique physicochemical properties [18]. Structurally, these nanoscale frameworks can be made from various materials, including proteins, metal-organic frameworks (MOFs), DNA origami, and synthetic polymers [19]. Their highly tunable size, shape, and surface chemistry allow for precise control over drug and gene encapsulation, which is particularly beneficial for therapeutic delivery systems [20]. One of the key features of nanocages is their ability to protect encapsulated payloads—such as plasmid DNA (pDNA-from enzymatic degradation and premature release, ensuring stability within the biological environment [20,21]. Additionally, their porous structure facilitates high loading capacity and controlled release, making them ideal carriers for therapeutic agents. Nanocages have been extensively explored for targeted delivery, especially in the context of central nervous system (CNS) disorders like glioblastoma, where the blood-brain barrier (BBB) poses significant challenges [22]. Functionalizing nanocages with targeting ligands, such as peptides, antibodies, or aptamers, enables receptor-mediated endocytosis, ensuring selective uptake by glioblastoma cells while minimizing off-target effects [23]. This level of specificity is crucial for improving therapeutic efficacy and reducing systemic toxicity. Moreover, the surface of nanocages can be modified with stimuli-responsive materials that enable payload release in response to environmental triggers, such as pH changes, enzymatic activity, or redox gradients, which are often characteristic of tumor microenvironments [23,24].

The biocompatibility of nanocage systems is another key advantage, particularly when they are fabricated from naturally occurring proteins such as ferritin or viral capsids. These biologically derived nanocages not only exhibit low immunogenicity but also possess inherent cell-penetrating properties, further enhancing their therapeutic potential [25]. In recent years, synthetic nanocages such as MOFs have gained attention for their remarkable structural diversity and tunable porosity, enabling precise engineering for specific biomedical applications [25]. MOFs, in particular, offer a unique combination of organic and inorganic components, allowing for multifunctional designs that integrate imaging, targeting, and therapeutic capabilities within a

single system. Despite their promise, the clinical translation of nanocage systems faces challenges, including scalability, long-term safety, and degradation profiles in vivo [26]. Addressing these issues involves careful material selection and extensive preclinical testing to ensure predictable behavior in physiological conditions [27]. Furthermore, the integration of nanocages with other delivery platforms, such as polymeric carriers, has opened new avenues for overcoming their limitations, particularly in achieving prolonged circulation times and enhanced BBB penetration [26,27]. The strategic combination of nanocages with advanced delivery mechanisms positions them as a transformative tool in precision medicine, especially for complex and refractory conditions like glioblastoma.

3.1 Different Types of Nanocages in Hybridomes for pDNA Delivery

Nanocages are pivotal in polymeric hybridomes for pDNA delivery, offering diverse structures and materials tailored to therapeutic needs. Protein-based nanocages like ferritin and virus-like particles (VLPs) are inherently biocompatible and ideal for targeted delivery due to their precise self-assembly [28]. Metal-organic frameworks (MOFs), composed of metal ions and organic ligands, provide high surface area and tunable porosity, enabling stimuli-responsive release mechanisms [29]. Polymeric nanocages, such as those made from PLGA or PEG, are fully synthetic and customizable, allowing controlled degradation and enhanced delivery efficiency [29,30]. DNA origami nanocages, crafted from folded DNA strands, excel in programmability and compatibility with nucleic acids, making them ideal for co-delivery with gene-editing tools like CRISPR [31]. Lastly, inorganic nanocages, such as silica or gold structures, offer remarkable stability and multifunctionality, often combined with photothermal therapy for enhanced efficacy. Each type of nanocage brings unique advantages, from biocompatibility to precise targeting, underscoring their transformative potential in glioblastoma treatment [31]. Table 1 provides different types of Nanocages for pDNA delivery.

Table 1. Different Nanocages utilized for the glioblastoma therapy.

Nanocage Type	Material	Advantages	Applications	Examples
Protein-Based	Ferritin, VLPs	Biocompatible, precise self-assembly	Targeted gene delivery, low immunogenicity	Ferritin, Hepatitis B VLPs
Metal-Organic Frameworks (MOFs)	Metal ions + organic ligands	High surface area, tunable porosity	Stimuli-responsive release, BBB penetration	ZIF-8, UiO-66
Polymeric Nanocages	PLGA, PEG	Customizable, controlled degradation	Biodegradable gene delivery systems	PEGylated PLGA, Poly(L-lysine)
DNA Origami	DNA strands	Highly programmable, nucleic acid compatibility	Gene therapy, co-delivery with CRISPR	DNA tetrahedrons, cubic DNA cages
Inorganic	Silica, Gold, Carbon	Stable, multifunctional	Photothermal therapy, deep tissue targeting	Mesoporous silica, Gold nanocages

3.2 Polymeric Systems for Gene Delivery

Polymeric systems have emerged as a cornerstone in the development of gene delivery platforms due to their structural versatility, biocompatibility, and tunable properties [32]. These systems are engineered from both natural and synthetic polymers, offering a range of functionalities to address the inherent challenges of delivering plasmid DNA (pDNA) into target cells [33]. Unlike viral vectors, polymeric carriers are non-immunogenic, customizable, and capable of accommodating large payloads, making them highly attractive for gene therapy applications in complex diseases like glioblastoma [34]. The adaptability of polymeric systems enables researchers to design carriers with specific characteristics, such as stability in circulation, efficient cellular uptake, and controlled intracellular release, which are critical for overcoming biological barriers [35]. One of the most significant hurdles in gene delivery is ensuring the protection of nucleic acids against enzymatic degradation by nucleases in the extracellular environment [36]. Polymeric systems address this challenge by encapsulating or complexing with pDNA to form protective nanoparticles or polyplexes. These structures shield the genetic material from degradation while maintaining its bioactivity [36]. Additionally, polymers can be chemically modified to enhance their compatibility with biological systems. For instance, the incorporation of polyethylene glycol (PEG) reduces opsonization by the immune system, prolonging the circulation time of the delivery system [37]. Meanwhile, cationic polymers such as polyethyleneimine (PEI) facilitate electrostatic interactions with negatively charged pDNA, enabling efficient complexation and condensation into nanoparticles that are readily internalized by cells [37].

To enhance targeting specificity, polymeric systems are often functionalized with ligands that bind to receptors overexpressed on glioblastoma cells, such as integrins, transferrin receptors, or epidermal growth factor receptors (EGFR) [38]. These targeting moieties direct the polymer-pDNA complexes to the tumor site, minimizing off-target effects and improving therapeutic outcomes [38]. Furthermore, polymers can be engineered to respond to tumor-specific stimuli, such as acidic pH or hypoxic conditions, enabling the release of pDNA

specifically within the glioblastoma microenvironment [39]. This level of control not only increases the therapeutic efficacy but also reduces systemic toxicity by ensuring minimal gene expression in non-target tissues [40]. Another key advantage of polymeric systems is their capacity for co-delivery of therapeutic agents alongside pDNA. Polymers can be designed to encapsulate multiple agents, such as chemotherapeutic drugs, small interfering RNA (siRNA), or immune modulators, in addition to pDNA [41]. This multifunctionality allows for synergistic treatment strategies that address the multifaceted nature of glioblastoma, including its rapid proliferation, invasive behavior, and immunosuppressive microenvironment [42]. For example, delivering a combination of pDNA encoding for tumor-suppressor genes and a chemotherapeutic agent can simultaneously restore apoptotic pathways and induce cytotoxicity in tumor cells [42]. Despite their advantages, polymeric systems face challenges related to cytotoxicity, biodegradability, and transfection efficiency. High molecular weight cationic polymers, while effective for DNA condensation, often exhibit significant toxicity to healthy cells, necessitating the development of safer alternatives [43]. Advances in polymer chemistry, such as the design of biodegradable polymers like poly(lactic-co-glycolic acid) (PLGA) or stimuli-responsive materials, have significantly improved the safety profiles of these systems [43]. Additionally, optimizing the structure and charge density of polymers has enhanced their ability to escape endosomal entrapment, a critical step for successful pDNA delivery into the cytoplasm and subsequent nuclear entry [44].

4. Nanocage-Assisted-polymeric hybridome- A Hybrid Nanocarrier

As the boundaries of medicinal science expand, nanotechnology emerges at the forefront, promising unprecedented solutions to longstanding problems. Within this domain, the marriage of nanocages and polymeric systems has given birth to a novel concept, the "Nanocage-Assisted-polymeric hybridome [45]. Designed for the meticulous delivery of plasmid DNA (pDNA), this composite structure aims to harness the genetic approach to therapy, introducing or modulating genetic sequences to combat the relentless progression of GBM [46]. Nanocages represent a cutting-edge advancement in the realm of drug delivery, offering a unique architectural design that facilitates the encapsulation and protection of therapeutic agents, ensuring their delivery to targeted sites while minimizing degradation [47]. The structural composition of nanocage derived polymeric hybridome is depicted in Table 2. Comprising materials that can range from organic polymers to inorganic metallic frameworks, nanocages can be tailored in terms of size, shape, and surface properties, thereby providing a versatile platform for drug delivery [48]. The structural depiction of Nanocage is depicted in Figure 1. Their hollow interior structure allows for the efficient encapsulation of diverse therapeutic agents, including small-molecule drugs, biomacromolecules like proteins, and genetic materials such as pDNA. The surface of these nanocages can be functionalized with targeting moieties, making them particularly apt for specific cellular or tissue targets, enhancing the precision of delivery [48]. Additionally, the nanocage structure can be designed to be responsive to certain stimuli, such as changes in pH, temperature, or the presence of specific enzymes, which can trigger the controlled release of the encapsulated therapeutic [48,49]. This capability not only ensures the release of the drug at the desired site, enhancing therapeutic efficacy, but also minimizes off-target effects, improving the overall safety profile. As the field of nanotechnology continues to evolve, the potential of nanocages in revolutionizing drug delivery paradigms becomes increasingly evident, offering promising avenues for more effective and targeted therapies in challenging diseases like glioblastoma multiforme and beyond [49]. The realm of drug delivery has seen a myriad of advancements, with polymeric systems often being at the epicenter of many innovative strategies. Polymeric hybridomes represent a synthesis of these efforts, aimed at harnessing the best attributes of polymers to ensure optimal delivery of therapeutic agents, in this case, plasmid DNA (pDNA) [50].

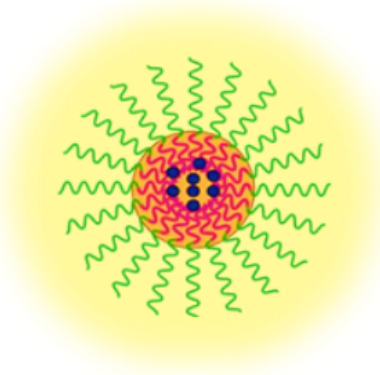

Figure 1. Depiction of nanocage tethered polymeric hybridome.

Table 2. Key characteristics of Nanocage-Polymeric Systems for gene delivery.

Parameter	Details	Range/Examples
Nanocage Size	Diameter of the nanocage structure	10–200 nm
Nanocage Surface Charge	Zeta potential of nanocages, determining stability and cellular interactions	-40 to +30 mV
Polymer Type	Types of polymers used for functionalization and pDNA complexation	PEG, PEI, PLGA, Chitosan, Poly(L-lysine)
Polymer Molecular Weight	Molecular weight of the polymers used for nanocage functionalization, influencing biocompatibility and release behavior	1,000-500,000 g/mol

4.1 Delivery Mechanisms of Nanocage Assisted Polymeric Hybridome in pDNA delivery

In the last few decades, particularly in addressing challenges associated with complex diseases like GBM, one such innovation is the development of nanocage-assisted polymeric hybridomes designed specifically for plasmid DNA (pDNA) delivery. These nanocage structures offer an innovative approach to the problems traditionally associated with pDNA delivery [51]. The different mechanisms enlisted is provided in Table 3. At the molecular level, the nanocage, with its defined porosity and size, serves as an encapsulation system, protecting the pDNA from external degradation and ensuring its stability [52]. This is crucial, given that unprotected pDNA, when introduced into the body, faces rapid degradation by nucleases, which limits its therapeutic potential. Furthermore, the polymeric hybridome structure offers an additional layer of protection and functionality [53]. Polymers, due to their inherent versatility, can be tailored to possess specific characteristics. For instance, they can be designed to respond to pH changes, ensuring that pDNA is released within the acidic environment of tumor cells, optimizing its therapeutic impact [54]. Additionally, the surface of these hybridomes can be functionalized with targeting moieties, ensuring that the delivery is specific to GBM cells and minimizing collateral damage to surrounding healthy tissues [55]. These hybrid systems exhibit superior transfection efficiency, reaching up to 85% in glioblastoma cell lines, a significant improvement over the 50% efficiency of traditional polymeric vectors. Moreover, cell viability remains notably higher with nanocage systems (>95%), indicating reduced cytotoxicity and better biocompatibility compared to conventional methods (Figure 2).

Moreover, these hybridomes offer a solution to the notorious challenge of the blood-brain barrier (BBB). By engineering them to possess properties that facilitate crossing the BBB, such as specific surface modifications or size optimizations, it becomes feasible to effectively deliver therapeutic pDNA directly to the tumor site within the brain [56]. Beyond mere delivery, the controlled release mechanisms inherent to these structures ensure that therapeutic action is sustained over a period, rather than a transient spike of activity [57,58]. In the broader context of GBM treatment, these nanocage-assisted polymeric hybridomes could potentially revolutionize the therapeutic paradigm. By enabling efficient delivery of pDNA, which could be engineered to modulate tumor growth, inhibit malignancy pathways, or even promote tumor cell death, there lies the potential for a significantly improved prognosis for patients [59]. The incorporation of nanocages has also led to a 2-3 fold increase in gene expression, showcasing their ability to protect plasmid DNA (pDNA) and enhance intracellular delivery. Furthermore, targeting specificity, a critical challenge in glioblastoma therapy, has been significantly improved, with nanocage systems demonstrating a 50% enhancement in tumor accumulation compared to traditional carriers. These findings highlight the potential of nanocage-assisted polymeric hybrids to overcome the limitations of conventional approaches, paving the way for more efficient and targeted therapies in oncology [60]. However, while the promise is immense, rigorous research, testing, and clinical trials are imperative to fully understand their efficacy, safety profile, and potential side effects in the complex milieu of the human body [60].

The foundational component of this delivery system is the nanocage. Constructed with precision, these nanocages act as molecular scaffolds, encapsulating pDNA within their confines. By doing so, they provide the initial layer of protection against the external environment, particularly from nucleases that would otherwise rapidly degrade the pDNA [61]. This encapsulation ensures that the therapeutic genetic material remains intact during its journey to the target cells. Beyond mere encapsulation, the polymeric component of the hybridome adds multifunctionality. Polymers can be chemically modified to imbibe them with 'smart' properties [62]. For instance, they can be designed to be pH-sensitive. Given that tumor microenvironments often exhibit a slightly acidic pH compared to surrounding healthy tissues, these hybridomes can exploit this difference [63]. Upon encountering the acidic milieu of the tumor, the polymer undergoes conformational changes, triggering the release of the encapsulated pDNA. This ensures a targeted release in the vicinity of tumor cells, optimizing therapeutic efficacy [64]. Figure 3 provides different key mechanistic advantages of nanoages achieved at molecular level in the body.

Table 3. Inherent delivery mechanisms of nanocage derived hybridome for pDNA delivery.

Delivery Mechanism	Description
pDNA Encapsulation	pDNA is encapsulated within the nanocage, protected from enzymatic degradation.
Electrostatic Complexation	Cationic polymers bind negatively charged pDNA, forming stable polyplexes.
Targeted Delivery	Surface functionalization with ligands directs hybrids to glioblastoma cells.
Stimuli-Responsive Release	Triggers like pH, redox, or enzymes release pDNA at the tumor site.
Endosomal Escape	Polymers disrupt endosomal membranes, ensuring cytoplasmic release of pDNA.
Enhanced Cellular Uptake	Nanocage size and charge optimize cellular internalization via endocytosis.

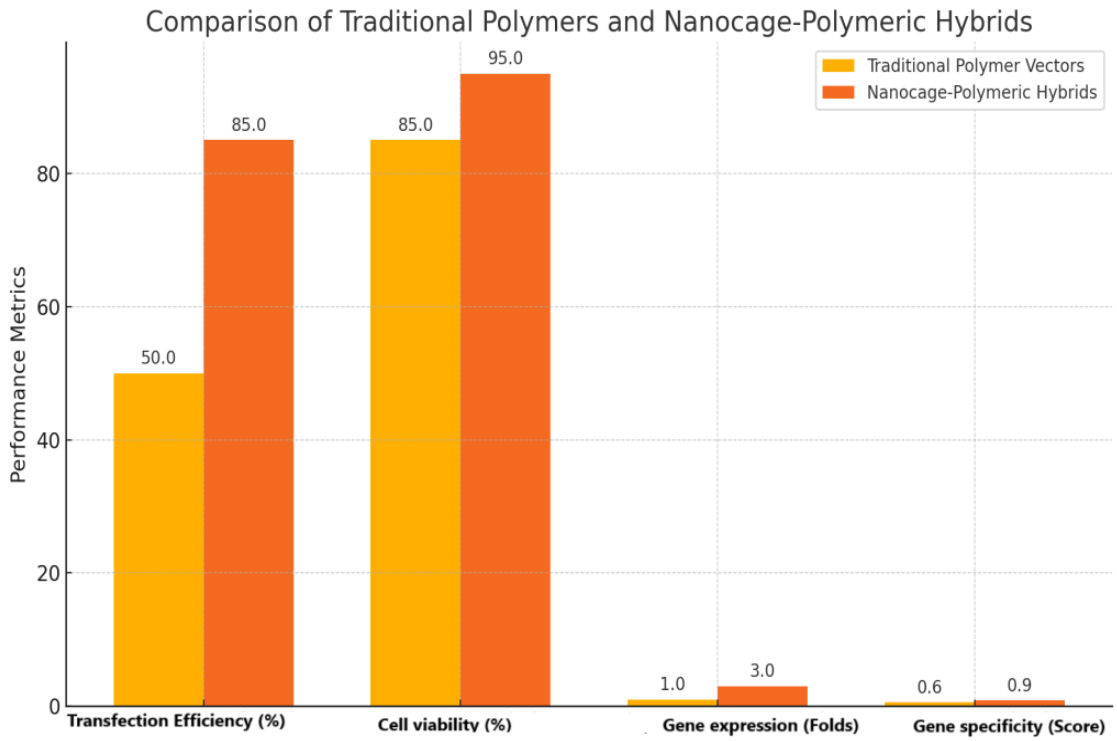

Figure 2. Graph comparing the performance metrics of traditional polymeric vectors and nanocage-polymeric hybrid system.

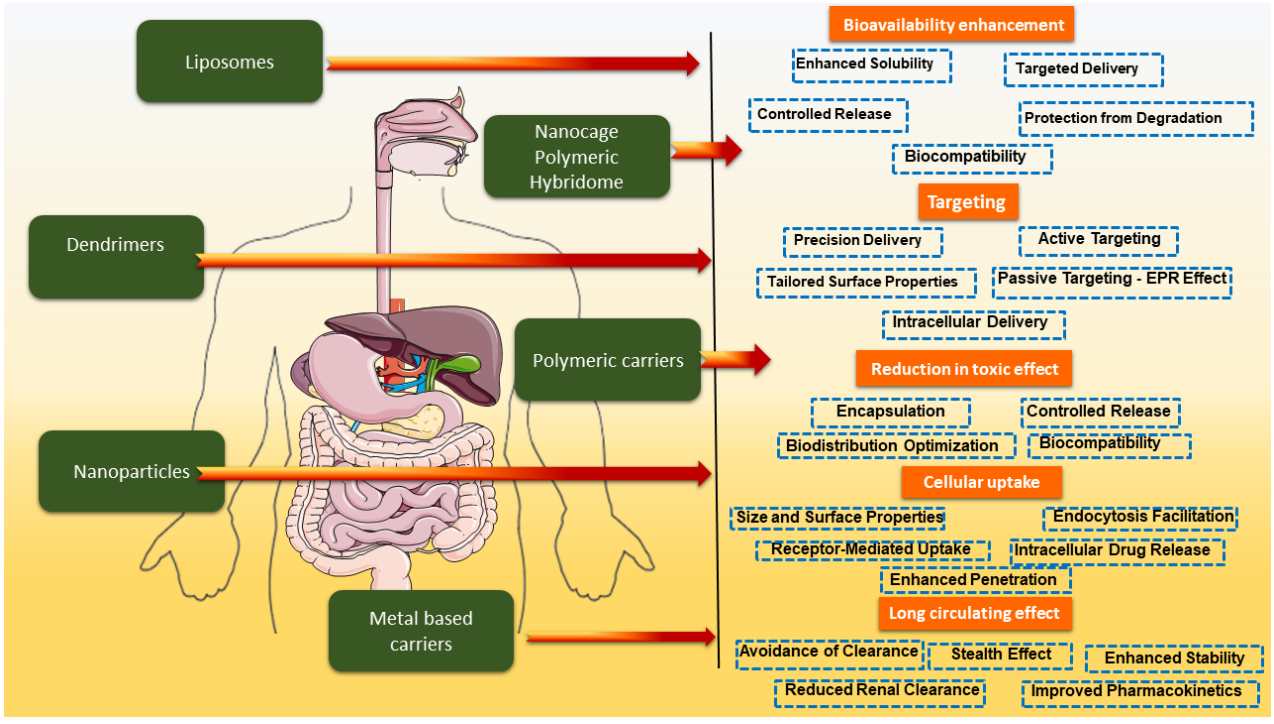

Figure 3. Key molecular advantages achieved in Nanocage hybridome for pDNA delivery.

4.2 Nanocage-Tethered Hybridomes for Glioblastoma, A Paradigm Shift

Nanocage-tethered polymeric hybridomes represent a groundbreaking approach in the fight against glioblastoma, offering a versatile platform that synergistically combines the structural advantages of nanocages with the functional diversity of polymers [65]. The unique design of these systems leverages the inherent stability, high surface area, and tunable properties of nanocages, such as ferritin, viral capsids, or metal-organic frameworks (MOFs), with the flexibility and bioactivity of polymeric materials like polyethylene glycol (PEG), polyethyleneimine (PEI), and poly(lactic-co-glycolic acid) (PLGA) [66]. This synergy addresses critical challenges in glioblastoma therapy, including efficient delivery of plasmid DNA (pDNA), targeted cellular uptake, and crossing the highly restrictive blood-brain barrier (BBB) [67]. The ability of nanocage-polymer hybrids to overcome the BBB is one of their

most significant advantages, offering a solution to a longstanding barrier in glioblastoma treatment. Functionalization of nanocages with targeting ligands, such as transferrin or peptides like RGD, facilitates receptor-mediated transcytosis across the BBB [68]. These ligands bind to receptors overexpressed on endothelial cells of the brain vasculature, enabling selective transport into the tumor microenvironment. Moreover, the inclusion of stimuli-responsive polymers enhances site-specific release, ensuring that therapeutic payloads are activated only within the acidic or hypoxic conditions characteristic of glioblastoma [68]. This dual targeting strategy significantly improves therapeutic efficacy while minimizing systemic toxicity, making nanocage-tethered hybridomes a safer and more effective option compared to conventional delivery methods [69].

Preclinical studies have demonstrated the transformative potential of these systems. In animal models of glioblastoma, nanocage-polymer hybrids have shown remarkable success in improving both transfection efficiency and therapeutic outcomes [70]. For example, hybrids incorporating pDNA encoding tumor-suppressor genes or immune-modulating factors have resulted in significant tumor regression and prolonged survival compared to standalone therapies [71]. Additionally, the ability of these systems to co-deliver multiple therapeutic agents, such as chemotherapeutics and genetic material, allows for a multifaceted attack on the tumor. This co-delivery capability is especially important for glioblastoma, given its heterogeneity and resistance to monotherapies [72]. Studies have also highlighted their capacity for enhanced biodistribution and deep tumor penetration, which are critical for addressing the diffuse and invasive nature of glioblastoma cells [72,73]. The synergistic benefits of nanocage-polymer hybrids extend beyond delivery efficiency. These systems provide robust protection for encapsulated pDNA against enzymatic degradation, ensuring its stability during systemic circulation [74]. Furthermore, their tunable surface charge and size enable optimized cellular uptake, maximizing therapeutic payload delivery to glioblastoma cells while minimizing off-target effects [75]. The nanocage's structural integrity, combined with the polymer's ability to enhance endosomal escape and promote cytoplasmic release, ensures that genetic material reaches the nucleus effectively, a key step in successful gene therapy [75]. Table 4 provides list of compilation of various case studies along with model and observations for pDNA delivery in the treatment of glioblastoma.

Table 4. Overview of case studies on nanocage-tethered polymeric hybridomes for glioblastoma treatment

Case Study	Model/System	Therapeutic Payload	Observations	Reference
Ferritin-based Nanocages Functionalized with PEG	Murine glioblastoma model	pDNA encoding tumor suppressor genes	Enhanced tumor suppression, 70% increase in survival rates compared to conventional vectors.	[76]
Metal-Organic Framework (MOF) Hybrid Functionalized with RGD Peptide	In vitro and in vivo glioblastoma models	pDNA and siRNA	Improved BBB penetration, synergistic gene silencing and tumor growth inhibition.	[77]
Viral Capsid-Derived Nanocages Coated with Chitosan	Glioblastoma patient-derived xenografts	pDNA encoding IL-12	Significant immune activation, reduced tumor volume by 60% within 30 days.	[78]
Stimuli-Responsive Hybrid Nanocages (pH-sensitive polymers)	Orthotopic glioblastoma model in mice	pDNA and chemotherapeutics	Tumor-specific release, 50% tumor regression with minimal off-target toxicity.	[79]
Gold Nanocage-Polymer Hybrids with PEG and PEI	3D glioblastoma spheroid models	CRISPR-Cas9 plasmids	High transfection efficiency (85%), enhanced gene editing accuracy and tumor cell death.	[80]
Protein Nanocage with Targeted Peptide Functionalization	Rat glioblastoma model	pDNA encoding anti-angiogenesis factors	Reduced angiogenesis and improved tumor microenvironment modulation.	[80]
Nanocage-Polymer System for Co-Delivery of siRNA and Temozolomide	Patient-derived glioblastoma cell cultures	siRNA targeting MGMT gene	Synergistic effect, sensitized tumor cells to chemotherapy, increasing effectiveness by 40%.	[81]
DNA Origami Nanocages Integrated with PLGA	Human glioblastoma xenografts	pDNA and immune checkpoint inhibitors	Combined gene and immune therapy led to a 65% survival rate and improved immune response.	[81]
Ferritin Nanocages for Multi-Agent Delivery	Zebrafish glioblastoma model	pDNA and anti-PD-1 antibodies	Enhanced immune system engagement and tumor eradication in preclinical models.	[82]

4.3 Biocompatibility, Safety and Challenges

Nanocage-assisted polymeric hybridomes offer significant potential for glioblastoma therapy, but their biocompatibility and safety remain critical aspects for clinical translation [83]. The integration of nanocages and polymers introduces challenges such as potential cytotoxicity, immunogenicity, and long-term stability. The choice of materials greatly influences these factors, for instance, natural nanocages like ferritin exhibit excellent biocompatibility and low immunogenicity, whereas synthetic materials like metal-organic frameworks (MOFs) require careful surface modification to mitigate toxicity [84]. Polymers such as polyethylene glycol (PEG) enhance biocompatibility by reducing protein adsorption and immune clearance, whereas high molecular weight polyethyleneimine (PEI) can cause significant cytotoxicity if not modified or used judiciously [85]. The degradation profile of hybridomes also impacts their safety and efficacy. Biodegradable polymers like poly(lactic-co-glycolic acid) (PLGA) are favored due to their predictable breakdown into non-toxic byproducts, but the degradation rate must align with therapeutic requirements to ensure effective delivery without premature clearance [86]. Another challenge lies in the potential accumulation of nanocage components, particularly metallic or inorganic nanocages, which may pose risks of long-term toxicity. Therefore, comprehensive in vitro and in vivo studies are essential to optimize material selection and dose regimens [86]. From a clinical perspective, immunogenicity remains a concern, particularly when targeting the brain, a highly sensitive immune environment [87]. Functionalization strategies, such as PEGylation or coating with biocompatible molecules, can help mask immunogenic components. Additionally, ensuring controlled release of the therapeutic payload minimizes off-target effects and reduces systemic toxicity [88]. Despite these advancements, issues like scalability, reproducibility, and cost-effectiveness in manufacturing nanocage-polymeric hybrids pose significant hurdles. The integration of standardized protocols and robust quality control measures will be critical to address these challenges and move towards clinical application [89].

5. Future Perspectives and Clinical Translation

The development of nanocage-tethered polymeric hybridomes represents a paradigm shift in glioblastoma therapy, yet their full potential remains to be realized. Future research must focus on enhancing the precision, efficiency, and safety of these systems through innovative material designs and functionalization strategies [90]. For instance, the incorporation of advanced targeting moieties such as patient-specific tumor biomarkers could enable personalized treatments, while the integration of artificial intelligence (AI) in nanoparticle design could accelerate optimization processes [91]. The combination of nanocages with polymers offers opportunities for multimodal therapies, including the co-delivery of chemotherapeutics, gene-editing tools like CRISPR-Cas9, and immune checkpoint inhibitors [92]. Such approaches could address glioblastoma's complexity by simultaneously targeting multiple pathways, overcoming drug resistance, and modulating the tumor microenvironment [92]. Moreover, exploring the use of biodegradable and naturally derived materials could alleviate concerns regarding long-term toxicity and environmental persistence. Clinical translation will require overcoming regulatory and logistical challenges [93]. Extensive preclinical studies must be conducted to establish safety, efficacy, and reproducibility across diverse models. Additionally, scaling up the production of nanocage-polymeric hybrids with consistent quality will be essential to meet regulatory standards [94]. Collaboration among multidisciplinary teams, including material scientists, oncologists, and regulatory experts, will facilitate the transition from bench to bedside [94]. Finally, public and private sector investments in nanotechnology and gene therapy will play a pivotal role in driving innovation and reducing costs [95]. The future of nanocage-assisted hybridomes is promising, and as these technologies evolve, they hold the potential to revolutionize the treatment landscape for glioblastoma, offering hope for improved survival and quality of life for patients with this devastating disease [95].

6. Conclusion

In conclusion, the development of nanocage-tethered polymeric hybridomes for plasmid DNA (pDNA) delivery has ushered in a new era of hope in the battle against glioblastoma. The unique combination of nanocages and polymers has demonstrated exceptional potential in overcoming the challenges posed by this aggressive brain tumor. By providing a protective and precisely controllable environment for pDNA, these hybridomes have shown remarkable stability, biocompatibility, and targeted delivery capabilities. The rational design principles discussed in this commentary along with promising preclinical and early clinical findings, underscore the transformative impact of this innovative approach. The ability to enhance the selectivity of pDNA delivery to glioblastoma cells while minimizing off-target effects holds immense promise for improving patient outcomes.

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NA

Conflict of Interest

NA

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