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Abstract

Full Text

Cell-penetrating peptides as a gateway for nanocarrier-mediated glioblastoma therapy

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ABSTRACT

The most virulent primary brain cancer is Glioblastoma Multiforme (GBM), which is defined mainly by poor survival and drug delivery failure as a therapy. The blood-brain barrier (BBB) restricts the passage of nearly all macromolecular drugs. The presence of a heterogeneous blood-tumor barrier (BTB) at invasive fronts is primarily accountable for recurrence location. This review helps in understanding the key role of CPP-functionalized Nanocarriers (NCs) in effective brain tumor targeting and crossing biological barriers. Conjugation of CPPs with NCs facilitates receptor-mediated transcytosis across the BBB and allows efficient endosomal release and targeted intracellular delivery within GBM cells and drug-resistant Glioma Stem Cells (GSCs). In addition, the review evaluates the hybrid platforms including CPP-liposomes, polymeric NCs, Dendrimers, and Inorganic NCs that utilize dual targeting and stimulus-responsive activation approaches for targeted delivery and synergy. Increased brain uptake and drug delivery by using the CPPs conjugated NCs are being viewed in preclinical studies. The novel synergy of peptide engineering and nanotechnology holds a distinctive potential to overcome both therapeutic resistance and delivery constraint, enabling efficient, personalized GBM nanomedicine.

Introduction

Glioblastoma multiforme (GBM) is a formidable challenge to contemporary medicine due to its malignant and fatal nature.1 GBM is a grade IV astrocytoma and constitutes about 52% of all primary brain tumors and 15% of all brain cancers and thus, one of the most prevalent and lethal Central Nervous System (CNS) tumors.2 The influence of GBM on humanity is strikingly represented through its epidemiological pattern, with an occurrence of 3.19–4.98 per 100,000 population annually, with a strong gender predominance in males by a ratio of 1.6:1.3 In spite of the intense research endeavor, GBM is a low median survival interval of 12–15 months, two-year survival is less than 30%, and five-year survival is extremely low at less than 10%.4 The treatment-free survival of the patients drops to only three months, and in most cases, it is seen that 91% of the patients experience failure of treatment, and 81% of the patients develop recurrence despite receiving advanced therapy.5 Multimodal therapy using surgery, radiotherapy, and chemotherapy is the prevailing standard treatment for GBM, but such conventional therapy is suffering from many drawbacks that are the cause of treatment failure.6 Because of the infiltrative tendency of GBM and the malignant cells being far beyond the apparently normal brain tissue from visible tumor margins, surgical treatment cannot be complete in resecting the tumor.7 Temozolomide (TMZ) is the most frequent chemotherapeutic drug used to treat GBM, but adaptation resistance is usually established during treatment. Reduced methylation ratios in recurrence are indicated in MGMT-methylated tumors that result in the formation of therapeutic resistance.8 In the same way, Radiotherapy also has severe limitations due to the GBM' s deadly nature despite increased doses of 90 Gy and the necessity for maintaining the healthful brain tissue.9 The other treatments, such as the application of Anti-angiogenic drugs (Bevacizumab), have been found to be effective but the outcome on the lines of survival is limited. Newer drugs like Regorafenib are superior to Lomustine but yield only partial gains.10 Keeping these severe limitations and inadequacies of conventional treatment modalities in view, the research fraternity has shifted towards the use of Nanocarriers (NCs) based drug delivery systems as a solution to combat therapeutic barriers in the treatment of GBM.11 Even though NCs have a number of benefits, including increased drug

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solubility, enhanced pharmacokinetics, and the ability to target drug delivery to tumor sites12; however, conventional NC systems face immense challenges that limit their effective clinical translation in the treatment of GBM.13 The existence of an impenetrable BBB restricts NC penetration and prevents more than 98% of small-molecule drugs and all macromolecular drugs from reaching brain tissue.14 Even nanoparticles that can cross the BBB encounter additional challenges, such as reduced tumor penetration, with reported maximum penetration depths of only 8–34 μm from blood vessels, which is insufficient to reach most tumor cells.15 In addition, plain NCs are rapidly cleared by the reticuloendothelial system, and intracellular delivery remains suboptimal even when target cells are reached.16 The enhanced permeability and retention effect, considered a putative advantage of NCs, has proven inadequate in GBM because of the heterogeneity of the blood–tumor barrier (BTB), where BBB-disrupted leaky vasculature in the tumor core is juxtaposed with an intact BBB at infiltrative rims.17 The identification of these intrinsic limitations has motivated several modifications to NCs over time, including the functionalization of NCs with cell-penetrating peptides (CPPs).

CPPs represent a new generation of short-sequence peptides with fewer than 30 amino acids, possessing a strong capacity to cross cellular membranes and deliver various molecules without causing long-term membrane damage. CPPs provide a flexible and efficient method of drug delivery through intracellular transport, with the ability to circumvent extracellular and intracellular barriers, whereas conventional drug-delivery methods rely largely on passive diffusion or receptor-mediated endocytosis.18 The major mechanisms by which CPP-mediated internalization of NCs is accomplished are energy-independent direct penetration and energy-dependent endocytosis.19 Recent studies report that CPP-functionalized NCs can significantly enhance BBB penetration and can be used to overcome key blockages in brain drug delivery.20 Compared with conventional drug-delivery methods, CPPs allow co-delivery with proteins, nucleic acids, and small molecules, and exhibit broad compatibility with active drugs.21 The mouldability of CPPs allows adjustments to enhance stability, specificity, and targeting efficiency through engineering with stimulus-responsive moieties that enable spatiotemporally controlled activation within the TME, potentially mitigating off-target effects and improving therapeutic efficiency.22 This review analyzes the translational value of CPP-functionalized NCs in GBM treatment through a critical assessment of preclinical and clinical data on CPP-mediated delivery of chemotherapeutic agents, gene therapy, and combination therapy. The concomitant use of CPPs and NCs offers diverse opportunities to overcome constraints in GBM treatment by addressing delivery limitations and therapeutic-resistance pathways. This combination is expected to improve patient outcomes through targeted and personalized therapeutic approaches.23

Physiological and pathological barriers in GBM

The existence of interlinked barriers that shield the tumor from therapeutic treatment and support persistent growth renders GBM extremely difficult to treat.2 The BBB and a highly immunosuppressive tumor microenvironment (TME) collaborate to inhibit drug penetration, impair therapeutic distribution, and challenge both traditional and novel treatment approaches.24 Knowledge of these barriers is essential for understanding why GBM is predominantly refractory to therapy and why novel strategies such as CPP-functionalized NCs have become promising methods for overcoming these challenges.25 The BBB is the most protective structure in human physiology, consisting of non-fenestrated endothelial cells held together by tight and adherens junctions, aided by pericytes, the basement membrane, and astrocyte end-feet, which together create the neurovascular unit.26 The pathophysiology of glioblastoma is characterized by invasive growth and diffuse invasion of adjacent brain tissue, producing a heterogeneous BTB in which pathological angiogenesis and vascular remodeling create a site of complex selective permeability.27 At the tumor core, hypoxia-induced endothelial growth and secretion of angiogenic factors such as VEGF induce proliferation of the microvasculature in the form of leaky vessels with lost barrier function.11 Yet at the infiltrative borders, where glioblastoma cells invade normal brain parenchyma, the BBB remains intact, generating a therapeutic contradiction whereby drugs can penetrate the tumor bulk but cannot reach the invasive cells that cause recurrence.28

This heterogeneity of barrier function has profound implications for therapeutic effectiveness. Even TMZ, among the limited number of chemotherapeutics that can cross the BBB, reaches concentrations in brain parenchyma of only 20% of the systemic dose owing to active efflux transporters, including P-glycoprotein and BCRP, which actively export therapeutic agents back into the circulation.29 The BBB in GBM has augmented permeability through IL-6/STAT3 signaling pathways, whereby differentiated tumor cells release more IL-6 than stem cells, causing STAT3 activation in endothelial cells and further downregulation of tight-junction proteins and efflux transporters.30 This creates spatially variable drug distribution that complicates uniform therapeutic coverage, with rapid washout from partially permeable zones explaining why systemically administered agents often underperform clinically despite demonstrating potent activity under laboratory conditions.31 The infiltrative pattern of GBM, involving tumor-cell migration into perivascular compartments and along white-matter tracts, further destabilizes the structure of the neurovascular unit while preserving selective barriers against sufficient drug penetration to these aggressively invasive cells.24

The GBM tumor microenvironment is a web of cellular and molecular elements that fosters tumor survival and therapeutic resistance through several interlinked mechanisms.32 Tumor-associated macrophages are the predominant components of the microenvironment, including resident microglia and infiltrating monocytes, which actively enhance angiogenesis, extracellular-matrix remodel-

ing, and suppression of T cells.33 This is worsened by regulatory T cells and myeloid-derived suppressor cells, which create an immunosuppressive environment that undermines immune-based therapies by secreting immunosuppressive cytokines such as TGF-β, IL-6, and IL-10, thereby slowing antitumor immune responses through direct inhibition of effector cells and indirect effects on antigen presentation. The immunosuppressive cytokine environment includes high concentrations of prostaglandin E2 and overexpression of STAT3 signaling, which serves as a convergence point for several protumorigenic pathways and thus potentiates immunosuppression and tumor-cell survival. This forms a vicious cycle in which the tumor actively remodels its microenvironment to escape immune surveillance and facilitate its own development and invasion.34

Aside from immune suppression, the structural organization of the GBM microenvironment itself is a major obstacle to drug delivery and distribution.27 The extracellular matrix, which is composed of hyaluronan and other glycosaminoglycans, is a dense meshwork that resists drug diffusion and presents mechanical barriers to drug penetration.30 Hypoxia typical of GBM induces production of VEGF and activation of matrix metalloproteinases, which enhances diffuse extension along perivascular and white-matter tracts, as well as the formation of acidic microenvironments capable of inactivating some therapeutics.35 Glioma stem cells located within perivascular niches introduce an additional layer of complexity because of their inherent resistance to standard therapies, resulting from high levels of efflux-pump expression and augmented DNA-repair mechanisms.36 These cells, although present in only a minority of the tumor-cell population, are responsible for tumor recurrence because they can seed into surrounding brain tissue and possess a multidrug-resistant phenotype.29 The consequence is inadequate penetration of hydrophilic drugs, heterogeneous distribution throughout tumor regions with differing barrier characteristics, and the development of "reserve sites" in which cancer cells become inaccessible to therapeutic intervention.34 These multifaceted barriers explain why GBM remains refractory

primarily to treatment approaches that have proven successful in other cancers, where the absence of the BBB allows for more straightforward drug delivery and where the tumor microenvironment may be less profoundly immunosuppressive.2 This insight has led the way in the creation of novel delivery strategies like CPP-functionalized NCs with the ability to simultaneously target both barrier systems through improved BBB penetration, specific tumor cell uptake, and possible intervention in the immunosuppressive microenvironment, holding promise for improving the therapeutic possibilities that have rendered GBM the most recalcitrant cancer to effectively treat.27

Cell penetrating peptides

CPPs tend to consist of a few amino acid residues that are able to cross cellular membranes without inflicting permanent harm. The high content of cationic arginine and lysine allows CPPs to electrostatically interact with anionic cell-

surface molecules like glycosaminoglycans and phospholipids. This first adsorption step accumulates CPPs at the membrane interface and prepares the following translocation steps. In addition to charge, amphipathic and hydrophobic substrates are often concomitant, allowing peptides to form α-helical or β-sheet structures that insert into lipid bilayers. Amphipathic helices orient polar faces towards aqueous environments and nonpolar faces into the membrane interior, causing local perturbation that allows passage. Hydrophobic CPPs, enriched with leucine, isoleucine, phenylalanine, or tryptophan, directly interact with lipid tails, reducing the energy barrier to insertion. To counterbalance aqueous solubility with affinity for lipids, CPPs usually have moderate overall hydrophobicity, as indicated by a GRAVY index of between 0.5 and + 0.5. Lastly, a preference to form structured secondary structures, e.g., helices or sheets, encourages ordered interactions with the bilayer and enhances the formation of transient pores or local membrane curvature. Collectively, these characteristics allow CPPs to deliver diverse cargos, such as proteins, nucleic acids, small molecules, and nanoparticles, across demanding biological barriers like the BBB, thus revealing therapeutic pathways unavailable to conventional delivery systems.

Mechanism of cellular internalization

The unique pattern of molecular interactions facilitates CPP-mediated cellular internalization and paves the way for the traversal of therapeutic agents past biological barriers, especially in cancer therapy. Comprehension of the process is needed in order to maximize delivery of drugs to targets like GBM, where the BBB and tumor-specific defenses need to be breached. Cancer cells present both challenges and opportunities for CPP-based delivery owing to their changed membrane composition, receptor profiles, and metabolic characteristics. Malignant transformation tends to enhance surface expression of negatively charged glycosaminoglycans and proteoglycans, providing a greater number of binding sites for cationic CPPs. In addition, cancer cells tend to overexpress certain receptors, including integrin αv$ $3 (targeted by RGD peptides), transferrin receptors, and LRP-1, which are amenable for targeted drug delivery.37 The acidity of the tumor microenvironment, at pH 6.5–6.8 compared to the normal pH of 7.4, provides opportunities for pH-responsive activation of CPPs. Several studies have designed "activatable" CPPs that are concealed under healthy conditions but become functional in acidic conditions by undergoing structural transformation or linker cleavage. In addition, cancer cells tend to exhibit higher levels of matrix metalloproteinase (MMP) activity, which can be utilized with MMP-cleavable linkers for inducing CPP activation in a tumor-selective manner. Some of the recent advances in cancer-targeting CPPs involve multifunctional approaches that integrate membrane penetration and targeting specificity. For instance, SAP(E) peptides conjugated with Doxorubicin (DOX) through glutathione-sensitive linkers allow targeted drug release within the reducing microenvironment of cancer cell cytoplasm, minimizing systemic toxicity.38

Likewise, pVEC-PEGA conjugates have exhibited a propensity to concentrate in breast tumor tissues, owing to their efficient membrane translocation and tumor-homing properties.39 The internalization process within GBM cells involves multiple distinct steps. Initially, targeting peptides such as Angiopep-2 bind to LRP-1 receptors present on brain endothelial cells, initiating transcytosis across the BBB. Once in the brain parenchyma, the CPP elements interact with glioma cell membranes by a range of mechanisms: electrostatic bonding to negatively charged components of the membrane, receptor binding to epitope-tagged overexpressed targets like integrin αv$ $3 by RGD motifs, and tumor-specific enzyme or pH activation.3

Recent research has demonstrated that glioma stem cells (GSCs), which play a role in tumor recurrence and therapy resistance, contain specific membrane properties that are amenable for targeting for delivery. These cells overexpress caveolin-1, so caveolin-mediated endocytosis is one of the important mechanisms of uptake. Furthermore, GSCs have elevated levels of ABC efflux transporters, highlighting the necessity for CPP systems that can defeat multidrug resistance mechanisms.40 Contemporary GBM-targeting approaches are now employing multifunctional nanoparticle platforms that are decorated with a variety of CPP types. Branco et al. (2024) described peptide strategies involving the combination of R8 CPP with cyclic RGD (cRGD) for both dual BBB crossing as well as glioma targeting, producing synergistic effects that more than doubled median survival in preclinical models.23 Likewise, transferrin-CPP dual-modified liposomes were found to cross the BBB, be well endocytosed by glioma cells, avoid lysosomal degradation, and deliver therapeutic payloads such as doxorubicin into the cytoplasm directly.41 With the incorporation of real-time tracking, new and detailed information regarding CPP behavior in GBM models has been presented. With the use of fluorescently tagged CPPs and modern imaging techniques, scientists have observed diverse uptake patterns in tumors, where CPP accumulation correlates with high MMP activity and low pH. Such findings have informed the design of new-generation CPP systems, which penetrate tumors more effectively and deliver drugs more uniformly.42

In conclusion, CPP-mediated cellular internalization is a sophisticated process. It can be tightly controlled for cancer and GBM-specific applications through appropriate peptide design, focused modifications, and environmental responsiveness. Continued innovations in these systems, fueled by an increasing mechanistic understanding and bolstered by advanced characterization methods, hold tremendous promise to overcome the major challenges in successful cancer therapy, particularly for brain cancers. Table 1 gives a concise summary of different CPP types utilized for improving cellular uptake for better therapies.

Categories of CPPs

CPPs are typically classified based on their dominant physicochemical properties, which determine both their mechanism and cargo compatibility. Four main categories are shown (Fig. 1):

Cationic CPPs

Cationic CPPs are the oldest and most researched membrane-translocating peptides. They consist of a dense cluster of positively charged residues, predominantly arginine and lysine, which electrostatically interact with negatively charged cell-surface proteoglycans and phospholipids. Prominent among them are the Polyarginine peptides, from the octaarginine (R8) peptide to longer polymers, which have an exceptionally high cellular uptake efficiency. Their high arginine content facilitates tight electrostatic and hydrogen-bond interactions with the cell membrane and makes them valuable vehicles for delivering diverse payloads, like doxorubicin into cancer cells and quantum dots into human A549 cells.43 Recent studies have progressed from merely employing these peptides to their advanced chemical modifications to improve performance.

Table 1
A brief overview of different categories of CPPs used for improved cellular uptake for effective therapies.

Sr.no.	Name of CPPs/platform	Findings	References
1	Cyclic Amphipathic Peptides (CAPs)	Facilitated efficient siRNA delivery and greater than 80% target gene knockdown, primarily through clathrin- and caveolin-mediated endocytosis. Efficacy correlated with binding affinity rather than cellular uptake.	60

Sr.no.	Name of CPPs/platform	Findings	References
2.	Cationic and Amphipathic CPPs	Developed as a non-covalent delivery system for mRNA, demonstrating effective cellular uptake and protein expression via electrostatic complexation. The presence of hydrophobic moieties and amino acid composition were found to be critical for transfection efficiency.	61
3.	Cationic Arginine-Rich Peptides (CARPs)	A novel class of neuroprotective agents with the ability to traverse the blood-brain barrier (BBB) and exhibit intrinsic neuroprotective properties, blurring the line between a delivery vehicle and a therapeutic agent.	62

Sr.no.	Name of CPPs/platform	Findings	References
4.	Lung Targeting Peptides (LTPs): S7A and R11A	Novel peptides that demonstrated robust transduction of human bronchial epithelial cells *in vitro* and mouse lung tissue *in vivo*. A cyclic version was found to be approximately 100-fold more efficient. Conjugated to SARS-CoV-2 siRNA for anti-viral efficacy.	63
5.	Hydrophobic Ion Pairs (HIPs) + Self-emulsifying Drug Delivery Systems (SEDDS)	A novel non-covalent formulation that enhanced the oral bioavailability of a peptide drug. The combination increased permeation by up to 57-fold in the Caco–2 cell model, with the HIP dissociating intracellularly for selective drug release.	64

Sr.no.	Name of CPPs/platform	Findings	References
6.	Drug-matched oligopeptide excipient platform (peptides designed to co-assemble with drugs into nanoparticles)	Enabled high-loading peptide–drug nanoparticles (up to 98% drug loading); improved drug solubility & stability; showed enhanced anti-tumor efficacy in acute leukemia models.	65
7.	CPPs for Antigen Delivery	Conjugation of CPPs with neoantigens was shown to enhance T cell priming and boost vaccine immunogenic-ity. Early clinical trials are underway for antigen-CPP vaccines.	66
8.	CL peptide (RLLRLLR polyarginine tail)	A cellular transmem-brane peptide that increased the transport of coupled small-molecule cargoes by about 10-fold.	67

Sr.no.	Name of CPPs/platform	Findings	References
9.	Pcp-oxal (octreotide-oxaliplatin)	A conjugate engineered to rapidly deliver the antitumor drug oxaliplatin into cells, improving intracellular delivery and enhancing anti-tumor activity *in vivo*.	68
10.	pH-sensitive Histidine-rich peptides (Hkd)	A peptide (Hkd) designed to selectively deliver the anticancer drug camptothecin to tumor cells in response to the acidic tumor microenviron-ment, reducing non-selective toxicity to normal cells.	69

Sr.no.	Name of CPPs/platform	Findings	References
11.	Protease-activated CPPs (ACPPs)	A class of peptides that become active upon cleavage by proteases like MMP-2 and -9, which are often overexpressed in tumors. This allows for targeted drug release and enhanced cellular uptake at the tumor site.	70
12.	Myristoylated peptides	This class of peptides showed a broad spectrum of antifungal activity against drug-resistant pathogens in an *in vivo* model and proved to be a potential candidate for antifungal agents.	71

Sr.no.	Name of CPPs/platform	Findings	References
13.	CPP-modified PLGA nanoparticles	Poly (lactic-co-glycolic acid) nanoparticles modified with CPPs demonstrated improved cellular internalization and provided solutions to peptide instability and enzymatic degradation, enabling controlled and targeted drug release.	72
14.	DNA-tagged Gold Nanoparticles	Gold nanoparticles conjugated with CPPs have enhanced cellular internalization and are being studied for targeted delivery, bioimaging, and theranostics.	73

Sr.no.	Name of CPPs/platform	Findings	References
15.	Trastuzumab-hsLMWP-BID fusion protein	An antibody-targeted fusion protein that leveraged a histidine-rich peptide to achieve endosomal escape and deliver the pro-apoptotic protein BID into cancer cells, demonstrating strong anti-tumor efficacy in a xenograft mouse model.	74
16.	Cardiac Targeting Peptide (CTP)	Delivered a therapeutic peptide to the heart via inhalation using a nano-in-micro technology, reversing cardiac remodeling and restoring systolic function in a porcine model of heart failure.	75

Sr.no.	Name of CPPs/platform	Findings	References
17.	CPP-functionalized Polymer Micelles	Improves deep tissue penetration and anti-tumor efficacy of drugs like paclitaxel by leveraging the enhanced permeability and retention (EPR) effect in breast cancer models.	76
18.	CPP-modified Liposomes (liposomes functionalized with cyclic, arginine-rich CPPs)	Cyclic CPP was coupled to the liposomal surface to enhance uptake and enable oral delivery of mRNA; it showed good stability, high mRNA loading, and cytocompatibility in intestinal models.	77

Sr.no.	Name of CPPs/platform	Findings	References
19.	Acylated pHD peptides	A pH-responsive peptide that forms nanopores in endosomal membranes upon acidification, enabling the cytosolic delivery of proteins and other macro-molecules.	69
20.	KRP-Hyd-DOX	A pH-responsive triggered drug delivery system that uses a hydrazone bond to release doxorubicin in the acidic environment of osteosarcoma cells, enhancing therapeutic efficacy.	78
21.	Octa-arginine (R8) with Methotrexate (MTX)	Conjugated to methotrexate to increase its bioavailability and overcome drug resistance in breast cancer cell lines.	79

Sr.no.	Name of CPPs/platform	Findings	References
22.	hPep peptides	A modified CPP that, when conjugated to methotrexate via a cathepsin B-cleavable linker, showed enhanced antiproliferative activity in drug-resistant breast cancer cells.	80
23.	Penetratin(desMet)-A with Methotrexate (MTX)	A modified CPP that, when conjugated to methotrexate via a cathepsin B-cleavable linker, showed enhanced antiproliferative activity in drug-resistant breast cancer cells.	79

Sr.no.	Name of CPPs/platform	Findings	References
24.	CPP-Nanocarrier Hybrid Platforms	A general strategy that leverages the properties of both components to overcome barriers like the mucus layer, immune clearance, and non-specific accumulation, enhancing drug accumulation at the target site.	48
25.	Gold Nanoparticles (Round) with DNA barcodes	Despite poor *in vitro* uptake, they were found to be excellent for tumor targeting *in vivo* because they were less likely to be cleared by the immune system.	73
26.	Gold Nanoparticles (Triangular) with DNA barcodes	Excelled at delivering therapeutic nucleic acids and heating tumor cells during photothermal therapy, with high cellular uptake *in vitro* and *in vivo*.	73

(continued on next page)

Table 1 *(continued)*

Sr.no.	Name of CPPs/platform	Findings	References
27.	Peptide Amphiphilic Molecules (PAs)	Can self-assemble into novel nanostructures, which are ideal for constructing nanodevices due to their adjustability and environmental responsiveness.	81
28.	Antigen-CPP Conjugates	Used to enhance antigen uptake by Antigen-Presenting Cells (APCs), leading to enhanced T cell priming and a boost in vaccine immunogenicity.	66
29.	Peptide Hydrogels	Used as a versatile biomaterial for wound management and as a carrier for biologically active substances like cells, growth factors, and drugs.	82

Sr.no.	Name of CPPs/platform	Findings	References
30.	Cell-Penetrating Peptides (general class, < 30 amino acids)	CPPs enable efficient intracellular transport of diverse molecular cargo across cell membranes without causing permanent damage; overcome extracellular and intracellular barriers; provide a versatile strategy superior to passive diffusion or receptor-mediated uptake; enhance nanocarrier-mediated therapy for GBM.	18

One key example is the use of a Boronic acid-functionalized cyclic deca arginine (cR10), specifically designed to enhance protein ubiquitin (Ub) delivery. Experimental data illustrated that the Boronic acid-linked cR10-Ub conjugate had about a fourfold enhancement of cellular uptake over the widely studied TAT-Ub conjugate. This advance represents a dramatic shift in the subject area. While the inherent cationic character of polyarginine is a point of departure, its potential is maximized by focusing chemical modifications with purpose to optimize membrane or cargo interaction. This methodology, merging advanced chemistry with delivery problems, is a shift from empirical approaches to rational molecu-

lar design.44 Transportan 10 (TP10) is a clinically well-characterized, lysine-rich chimeric cell-penetrating peptide with proven high efficiency in delivering nucleic acids and other large molecules. Its efficacy is partially due to its capacity to adopt an α-helical conformation at the cell membrane surface, facilitating cellular uptake. Nevertheless, similar to most initial CPPs, TP10 suffers from significant disadvantages: low specificity and cytotoxicity at physiological conditions, limiting its therapeutic application. As an excellent case study in modern peptide design, scientists developed a new pH-activated TP10 variant, TH, by replacing lysines with histidines. This switch drastically changed the behavior of the peptide. The TH peptide is less active and less toxic at physiological pH (7.4), when the histidines are protonated. In the acidic tumor environment (pH of about 6.0), the histidines become deprotonated, triggering the peptide and allowing it to penetrate cancer cells efficiently. The TH-camptothecin (CPT) conjugate displayed strong, pH-sensitive cytotoxicity against cancer cells, while being less toxic under normal physiological conditions. This innovation is a dramatic improvement in CPP design, illustrating the way a stimuli-responsive strategy can transform a potentially toxic, non-specific peptide into a targeted, safe therapeutic.45

Amphipathic CPPs

Amphipathic CPPs are composed of sequences that place hydrophilic and hydrophobic residues on opposite faces when adopting a helix, so they can engage simultaneously with the aqueous milieu and the lipid bilayer. Earliest examples like transportan and MPG have employed this amphipathic nature to deliver bulky protein payloads; however, there has been more recent advancement of the field by structure–function analysis and high-throughput screening. One study investigated the efficiency of the amphipathic CPP LAH5 in delivering the complicated CRISPR-Cas9 ribonucleoprotein (RNP) system, comprising Cas9, its single guide RNA (sgRNA), and a single-stranded HDR template required for gene editing precision.46 Likewise, the amphipathic CPP LAH5 was used as a delivery agent for the CRISPR-Cas9 ribonucleoprotein (RNP) system, which constitutes Cas9, single guide RNA (sgRNA), and a single-stranded HDR template required for gene editing with accuracy. The amphipathic peptide sC18 from the antimicrobial peptide cathelicidin has been explored as a potential anticancer drug development conjugate.47 A review of studies on structural modifications to sC18 demonstrated that the ability of the peptide to be

Fig. 1. Visual depiction of various CPP categories and their locations on nanocarrier surfaces, illustrating a general cellular uptake mechanism.

internalized is also vulnerable to where modifications are made in its sequence. A modification at position 15, for instance, was found to increase both total charge and cellular uptake, while other substitutions for charged residues with neutral amino acids lowered internalization.48 A research presented a new CPP with the amino acid sequence serine-isoleucine-tyrosine-valine (SIWV), which was highly capable of targeting glioblastoma brain tumors. Combined with porous silicon nanoparticles (psiNPs), such a system greatly enhanced selectivity

and therapeutic efficacy in mouse models, successfully penetrating the BBB to target the tumors. Development of the SIWV peptide is a major advancement, as it directly challenges the long-standing problem of non-specificity that has hampered clinical application of most CPPs. The peptide provides membrane penetration and targeted delivery, with the nanoparticle conferring stability and the capacity to deliver a therapeutic agent. This dual strategy has been an extremely successful method of creating more effective, targeted therapies that can cross more than one biological barrier to deliver us closer to personalized and precision medicine.49

3.2.3. Hydrophobic CPPs

Hydrophobic CPPs, while less frequent, primarily rely on nonpolar amino acids to insert into the lipid core and facilitate cargo transfer by mechanisms such as inverted micelle formation or reversible pore formation.

The model peptide pVEC, which is a derivative of vascular endothelial cadherin, demonstrates this strategy with the use of leucine and valine clusters for penetration through membranes independently of surface charge interactions.

Research on hydrophobic CPPs has focused on their intrinsic characteristics, particularly those arising from signal peptide-derived sequences like SG3 and Pep−7, which have been found to have a greater affinity with the hydrophobic portions of the membrane than with charged CPPs.50 An important recent development brings to the fore a significant paradigm shift in their application. The emphasis here is on the JM2 peptide, which extends beyond the general function of a CPP as merely a carrier; rather, JM2 is the therapeutic molecule itself. Derived from the connexin 43 protein, JM2 has an action by interfering in a key protein-protein interaction between microtubules and connexin 43. This process is central because it acts on treatment-resistant glioblastoma stem-like cells, which are a subpopulation of cells responsible for tumor recurrence. Preclinical work with JM2 is highly promising. This approach provides a more advanced and possibly more potent method to combat the complexity and heterogeneity of GBM.51,52

CPPs for GBM targeting

The therapeutic application of CPPs for treatment of GBM requires sophisticated engineering methods to overcome several biological obstacles while being selective and with minimal off-target effects.

Conjugation with Tumor-Homing peptides

This strategy entails covalently linking a CPP to a specific peptide or ligand that targets receptors overexpressed on the surface of GBM cells or the BBB.

This constitutes a dual-targeting system in which the homing peptide guides the nanocarrier to the tumor, and the CPP facilitates efficient cellular uptake.53 The Angiopep−2 peptide is a ligand of the low-density lipoprotein receptor-related

protein 1 (LRP−1), which is strongly expressed on brain endothelial and glioma cells. A system that incorporates both the CPP Tat and Angiopep−2 has been shown to significantly facilitate the crossing of a chemotherapeutic drug through the BBB and into a mouse intracranial glioblastoma model.54 Transferrin (T7) ligand interacts with the transferrin receptor, which is heavily distributed over the BBB and tumor cells. Tat-T7 double-decorated liposomes exhibited better tumor targeting and enhanced median survival of tumor-bearing mice compared to Tat or T7 single-decorated liposomes or free drug.55 Other peptides including BTP−7 and C1C2 have been engineered for the improvement of BBB permeability and targeting GBM.56

3.3.2. "Smart" and Stimuli-Responsive CPPs

These sophisticated systems are designed to remain dormant in healthy tissues and only become active to release their cargo when they sense the particular conditions of the TME.57 Glioblastoma cells proliferate unchecked and swiftly, developing a localized acidic microenvironment (low pH). Peptides can take advantage of this by including protonable amino acids, like histidine, in their sequences. Under physiological pH, the peptide is either neutral or has a low charge; however, in acidic TME, histidine residues get protonated, thus increasing the positive charge of the peptide and enhancing cellular uptake. This process guarantees drug release to largely happen at the tumor site, using pH-sensitive CPPs.58

Enzyme-Cleavable systems (ACPPs)

Most tumors, including GBM, secrete large quantities of specific proteases, e.g., Matrix Metalloproteinases (MMPs). Activatable Cell-Penetrating Peptides (ACPPs) are designed with a polycationic CPP region that is initially masked by a neutralizing polyanionic domain linked through a cleavable linker. When the ACPPs at the tumor site, elevated MMP activity cleaves the linker, exposing the CPP and allowing it to facilitate the delivery of the therapeutic cargo directly into the cancer cells. The inclusion of D-amino acids within the polycationic region of ACPPs also prevents nonspecific protease degradation within the bloodstream.59

CPPs-based nanocarriers in GBM

As a response to the severe obstacles in GBM therapy, nanotechnology has arrived as a revolutionary method for brain drug delivery.83 Nanoparticles, whose dimensions, surface characteristics, and constituents are tunable, function as a platform for drug carrier encapsulation, improving their solubility and stability in the bloodstream.84 More importantly, these nanoscale drug delivery systems can be engineered to cross the BBB/BBTB, enhancing drug penetration and allowing for targeted delivery directly to the tumor (Fig. 2). This approach greatly enhances local drug concentration in the tumor while also reducing systemic toxicity and minimizing damage to healthy cells.85 Conjugation of

CPPs onto the surface of nanoparticles has allowed scientists to actively facilitate the transport of therapeutic payloads through the BBB and into the brain parenchyma.49

CPP-decorated liposomes

Liposomes are one of the most thoroughly studied nanoparticles owing to their biodegradability, biocompatibility, and ability to encapsulate multiple drugs. Yet, their use of passive diffusion usually proves inadequate in crossing the BBB to induce therapeutic effects. To overcome this limitation, researchers have surface-modified liposomes with CPPs, allowing for active targeting and penetration across the BBB.86 In one study, two peptide ligands, namely Peptide−22 and the cyclic peptide c(RGDfK), were conjugated onto liposomes to target both BBB and glioblastoma simultaneously. Peptide−22 was utilized because it is a binder to LDLR on BBB endothelial cells. In parallel, c(RGDfK) was chosen for targeting the integrin $\alpha_v\beta_3/\alpha_v\beta_5$ receptors overexpressed on both the BBTB and glioblastoma cells. After loading with DOX, this dual-targeting system exhibited remarkably higher uptake in U87 glioblastoma cells and enhanced brain tumor distribution. The cooperative effect of the two peptides led to a significant prolongation of median survival in glioma-bearing mice to 39.5 days, a significant improvement over controls.87 Another study investigated a straightforward but potent cell-penetrating peptide, octa-arginine (R8), in enhancing liposome-based drug delivery. R8 is a cationic peptide and is recognized for its capacity to deliver a number of agents to the brain in vivo. The authors conjugated R8 to oleic acid-modified liposomes, which were subsequently filled with DOX at an impressive encapsulation efficiency of more than 95%. In U87-MG cell uptake studies, the R8-liposomes showed 8.6 times greater absorption than unmodified liposomes. In addition, in vivo studies in mice also indicated that R8-liposomes significantly enhanced DOX deposition in the brain, with the AUC at 2.4 times greater than that of unmodified liposomes. These results confirm the BBB-penetrating capability of R8 as a strong and

Figure annotations: A; B; C; Direct Penetration; Endocytosis; Endosome Escape; Cytosol Delivery; Cell Bursting; Cell Lysis; Higher Cell Penetration of Nanocarriers; Effective Treatment.

Fig. 2. Diagrammatic illustration of 2A shows different mechanisms responsible for the internalization of NCs inside GBM cells through BBB. 2B depicts various types of NCs surface-functionalized with CPPs. 2C illustrates higher penetration NCs surface-functionalized with CPPs leading to cell bursting or lysis, resulting in effective treatment.

efficient method for drug brain delivery enhancement.88 Liposomes can be native cationic and pass non-specific absorptive-mediated transcytosis due to their positive charge. Adding an easy-to-use cationic CPP like R8 boosts this approach, allowing for more controlled and efficient utilization of electrostatic forces to cross the BBB. The case of c(RGDfK)/Peptide-22 moves the concept one step further by incorporating receptor-mediated targeting, demonstrating a

trend from broad to very specific delivery approaches.89

CPP-conjugated polymeric nanoparticles

Polymeric nanoparticles are a versatile form of NCs, offering tunable characteristics like regulated and sustained drug release. Biocompatible biodegradable polymers, such as poly(lactic-co-glycolic acid) (PLGA), are particularly attractive because of their biocompatibility and FDA approval. When such polymeric scaffolds are functionalized with CPPs, researchers are creating sophisticated delivery systems capable of penetrating the BBB.90 A new study investigated the effect of surface density of Angiopep-2 (Ang-2) on penetration into the BBB. Ang-2 is a peptide ligand having high affinity for the LRP1 receptor, which is overexpressed on BBB endothelial cells and glioblastoma cells, and hence is amenable for targeted delivery. In conventional two-dimensional cell cultures, nanoparticle uptake consistently augmented as the density of Ang-2 increased density.91 A different study investigated a novel peptide, C1C2, for the production of multifunctional polymeric nanocarriers (NCs). Such polymer conjugates were prepared via reversible addition-fragmentation chain transfer (RAFT) polymerization, allowing for controlled manipulation of their structure and function. The C1C2 peptide was chosen because it targets the claudin-1 and claudin-2 proteins, which play an important role in the regulation of the blood-brain barrier (BBB) tight junctions. The system was engineered for both drug delivery and real-time imaging. The polymers were radiolabeled with copper-64 to enable non-invasive tracking of the distribution in the body. In mouse models, the C1C2-conjugated polymers exhibited significantly enhanced brain accumulation, with brain perfusion imaging validating their effective capacity for crossing the BBB.56 This research emphasizes the significant potential of these polymer-peptide conjugates in a targeted theragnostic strategy.

CPP-conjugated dendrimers

Dendrimers are a unique class of hyperbranched, monodisperse macromolecules with a structure that is precisely defined and provides them with remarkable stability in complicated biological media. In contrast to liposomes or polymeric nanoparticles, which are generally formed by self-assembly, dendrimers are synthesized chemically, building a robust structure that is resistant to degradation and premature drug release. Their highly tunable surface chemistry also renders them ideal for site-specific functionalization with CPPs to facilitate targeted delivery to the brain delivery.92 One of the greatest achievements in dendrimer-based therapy was the design of a poly(amidoamine) (PAMAM) dendrimer modified with two distinct targeting peptides. This platform was functionalized with Ang-2 to facilitate crossing the BBB by binding with the LRP1 receptor, which is overexpressed on brain capillary endothelial cells. Having crossed the barrier, the secondary payload of the nanocarrier was triggered by an Epidermal Growth Factor Receptor (EGFR)-targeting peptide, chosen for its affinity for the overexpressed EGFR on glioma cells. The dendrimer was also designed to deliver DOX and release it upon encountering the weakly acidic microenvironment of the tumor, which increases specificity and reduces damage to normal

tissue. The dual-targeting dendrimer possessed superb BBB penetration and glioma targeting in vitro and in vivo experiments, which markedly enhanced anti-glioma efficacy and prolonged the survival in the glioma mouse model.93 Taking advantage of the therapeutic potential of Ang-2, one study presented a fourth-generation polypropylene imine (PPI) dendrimer-based multifunctional nanotheranostic platform. The PEGylation of the nanocarrier was done to enhance biocompatibility and conjugated with ANG-2 to target glioblastoma cells. A salient aspect was the incorporation of silver sulphide (Ag2S) quantum dots that facilitated near-infrared (NIR) imaging for non-invasive, real-time monitoring of the distribution of the nanocarrier in vivo. The nanoscale system was loaded with the chemotherapeutic agent TMZ, which is standard treatment. Ex vivo experiments revealed greatly enhanced uptake and cytotoxic activity towards both BBB endothelial and C6 glioma cells relative to free TMZ. NIR in vivo biodistribution imaging revealed that there was greater accumulation of the nanocarrier in the tumor tissue.94

CPP-conjugated inorganic nanocarriers

Inorganic nanoparticles (INPs), including gold, silver, and iron oxides, constitute a heterogeneous material family with unique physical and chemical characteristics, rendering them applicable in therapeutic and diagnostic purposes. Conjugation with CPPs through INPs facilitates the creation of novel theranostic platforms that involve imaging,

drug delivery, and other treatments within one system.95 There are fewer reports documenting the application of gold nanoparticles (AuNPs) in theranostics. For example, AuNPs have also been functionalized with different cell-penetrating peptides (CPPs), including the NFL-TBS peptide, Vimentin (Vim) peptides, and the commonly used TAT peptide.96 Peptide internalization into cells was investigated in addition to the specific properties of gold particles, which allowed their imaging by electron microscopy to identify their location within organelles. Further, AuNPs also possess thermoplasmonic characteristics that render them useful for photothermal therapy, which involves the transformation of light energy to heat energy to harm and kill tumor cells.97 Recent studies have investigated the potential of AuNPs as a platform for theranostic platforms. In an intriguing study, AuNPs were conjugated with numerous CPPs such as the NFL-TBS peptide, Vimentin (Vim) peptides, and the renowned TAT peptide.96 The cell-penetrating ability of the peptides was combined with the unique properties of gold particles that allowed visualization by electron microscopy to track their position within organelles. AuNPs also possess thermoplasmonic properties that render them appropriate for photothermal treatment, a method that employs light to produce heat and specifically target cancerous cells.97 The constructed hybrid nanovectors displayed outstanding cellular uptake in glioblastoma cells and displayed remarkable stability.96 Another method in theranostic nanomedicine takes advantage of the FDA-approved cross-linked iron oxide nanoparticles (CLIO). Rather than the use of conventional CPPs for direct cellular uptake, it takes advantage of a complex, multi-step targeting

strategy to reach equally effective results.

The CLIO nanoparticles are conjugated to a vascular disrupting agent (VDA) named azademethylcolchicine (ICT2552) by means of an MMP-14-cleavable linker. MMP-14 is an enzyme enormously overexpressed in glioblastoma, thus representing a good activation target. The nanoparticles are constructed to accumulate in tumor tissue, where MMP-14 cleaves the linker to release the VDA. This process breaks down tumor vasculature and the BBB, inducing a feedback loop leading to further nanoparticle intake. The system selectively targets and kills glioblastoma initiating cells (GICs), which are quiescent cells that are the cause of radioresistance and recurrence of the tumor. MRI allows monitoring of delivery and accumulation in real time, and co-application of this nanocarrier with radiotherapy dramatically increases survival in glioblastoma-bearing mice.98

Dual/multifunctional nanocarriers

Synergy for Superior Efficacy Because of GBM' s complexity, such as multiple resistance pathways, heterogeneity in tumors, and immunosuppressive tumor microenvironment, a multi-faceted treatment strategy is necessary. Single-agent therapies also fail to effectively address such a complex disease. Consequently, an important nanomedicine trend is the development of dual and multifunctional nanocarriers which combine several drugs or targeting strategies in a single synergistic system.99 A new generation nanoliposome was engineered to augment Boron Neutron Capture Therapy (BNCT). This novel system not only brings a therapeutic compound to the target but also actively remodels the tumor microenvironment to enhance therapy efficiency. The nanoliposome was functionalized with the c(RGD) peptide to enhance its targeting towards the tumor. Furthermore, two enzymes, catalase (CAT) and lactate oxidase (LOX), were immobilized on its surface. As gliomas' TME is characterized by oxidative stress and hypoxia, these enzymes accelerate reactions that produce oxygen and decrease the level of lactic acid, hence reversing hypoxia. This environmental manipulation in conjunction with the boron-containing drug for BNCT resulted in a more potent anti-tumor response in both *in vitro* and animal experiments.100 This research presents an NC that not only modifies the biological environment to achieve better therapeutic effects but also simply applies treatment. A synergistic, dual-targeting approach with another example was the development of NCs through conjugating two separate peptides, Pep-1 and CREKA, to a PEG-PLGA platform. These NCs carried Paclitaxel. The peptides had complementary functions: Pep-1 supported crossing the BBB/BBTB by interleukin-13 receptor-$ $2-mediated endocytosis, while CREKA targeted fibrin-fibronectin complexes that are prevalent in the tumor microenvironment. The system greatly enhanced Paclitaxel' s cytotoxicity against U87MG cells and prolonged median survival time of mice bearing intracranial GBM to a whopping 61 days.101 A study pointed to the promise of a novel class of multifunctional nanocarriers: Ang-2 functionalized lipid cubosomes. Designed to deliver two chemotherapy drugs, Cisplatin and TMZ, within a single nanoplat-

form, these cubosomes feature an internal ordered inverse primitive cubic phase. Functionalized with Ang-2, they can cross the BBB and target delivery effectively. The system showed significantly increased uptake by U87 glioblastoma cells and greater brain accumulation in vivo compared to non-functionalized cubosomes. The combination of two drugs with distinct actions provides a powerful strategy to bypass resistance to individual drugs, and this nanocarrier showed a synergistic and more toxic effect against U87 cells spheroids.102

Challenges, limitations, and future outlook

Despite their great potential, translating CPP-based NCs into clinical use encounters several major hurdles. CPPs also have their limitations, such as limited transport effectiveness, often due to endosomal entrapment after they are taken up by cells, along with a lack of selectivity and instability in the bloodstream.53 The field has directly addressed these issues through sophisticated NC design. The use of PEGylation, for example, enhances serum stability and prolongs circulation time, thereby increasing the likelihood of a successful interaction with the BBB.103,104 Moreover, researchers are adding endosomolytic components to the nanocarrier to help the therapeutic payload escape from the endosome into the cytoplasm, which improves its effectiveness.93 The move toward complex, multi-component systems with stable covalent bonds directly addresses these inherent limitations, marking an evolutionary progression from simple peptide-cargo complexes to highly engineered nanoplatforms.105 In nanomedicine, there is no universal solution. The effectiveness of NCs relies heavily on their particular design features, such as size, shape, surface charge, and the density and type of conjugated ligands.106 The conflicting results from the Angiopep-2 density study, in which different in vitro models yielded opposite outcomes, emphasize a significant methodological challenge. This demonstrates that NC's effectiveness is not solely determined by its design but heavily relies on its interaction with a complex biological environment.105 Hence, future studies should aim to optimize these parameters with more physiologically relevant in vitro models, like BBB-on-a-chip systems, to improve the accuracy of in vivo performance predictions and prevent misleading preclinical outcomes.107 Although preclinical results are very promising, translating these advanced nanocomposites into clinical use faces significant hurdles. A key concern is the potential for long-term toxicity, especially with inorganic components, whose behavior and effects on the human body remain unclear. Additionally, achieving reproducible and cost-effective large-scale production is challenging. Complex synthesis techniques, like RAFT polymerization for polymeric nanocarriers or the precise attachment of multiple ligands to dendrimers, are often intricate and hard to scale up, which limits their commercial potential. Overcoming these issues is essential to shift these innovative platforms from research settings to clinical applications.106

Cell-penetrating peptide-functionalized nanocarriers present a tremendous paradigm shift in the treatment of glioblastoma multiforme. These studies

demonstrate such systems as highly effective in overcoming the formidable physiological barriers of the BBB and BBTB that, until now, have hampered traditional therapies. Not only can these platforms carry synergistic payloads, but they can also modulate the tumor microenvironment, enable real-time diagnostic imaging, and

target multiple disease markers simultaneously. It is increasingly apparent that the generation of advanced in vitro models must be established to better predict and optimize the performance of these complex nanocarriers. While there are still challenges ahead with long-term toxicity, reproducibility, and scalability, there is little doubt regarding the direction this field is taking. Future GBM treatment will be based on intelligent, multi-modal nanoplatforms able to precisely deliver powerful, combined therapies directly to the tumor—a truly new era in personalized, effective treatment for this terrible disease.

CRediT authorship contribution statement

Sagar Trivedi: Conceptualization. **Aditi Sonone:** Writing –original draft. **Mansi Thakur:** Writing –original draft. **Sapna Patel:** Validation. **Manisha Kawadkar:** Supervision. **Kamlesh Wadher:** Supervision.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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