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Multifaceted Peptide Based Nanoparticles for Diagnosis of Brain Tumors: Recent Advances and Future Outlooks

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Abstract

Novel drug delivery utilizes extremely penetrable nanoparticles for their ability to overcome defective bio-distribution to minor barricades like intracellular trafficking, especially the stubborn blood-brain barrier. Novel methods popularize them in therapy and diagnosis of tumors, neuro-degenerative disorders etc. Unstable individual peptide chains undergo 'self-assembly', triggered by various factors, yielding peptide-based nanoparticles with high bio-compatibility and hydrophobic properties leading to cell-penetrating peptides [CPPs], which initiate nanoparticle internalization. CPPs are modifiable pre- and post-assembly for enhanced target specificity and are capable of delivering therapeutics, proteins, nucleic acids, and imaging agents. Nanoparticles must also permeate the blood-brain and blood-cerebrospinal fluid barriers regulated by endothelial and epithelial cells. Oral route and increased positive charge cause high penetrability, efficacy and patient amenability while the intravenous route ensures maximum bio-distribution. Internalization may be energy-dependent or independent, and the enhanced permeability and retention (EPR) effect aids uptake and retention through malformed vessels. However, hemolytic potential can cause toxicity in some peptides. CPPs' are affected by structure, concentration, length, and charge, and when combined with nanomaterials, they exhibit increased bioavailability, stability, selectivity, and in-vivo efficacy. Slow nanoparticle neutralization could result in long-term toxicity. Advances include direct nanoparticle injection, real-time toxicity monitoring, and tumor-specific staining for improved therapeutic outcomes.

Keywords: Blood-brain barrier CPPs; Nanoparticles; Peptide-based nanoparticles; EPR effect

Introduction

Brain tumors are the heterogeneous group of neoplasms arising from uncontrolled cell proliferation within the cranial vault that poses significant threat to human health and longevity [1]. Despite various advancements in surgical techniques, radiotherapy, and chemotherapy, the prognosis for many brain tumor patients remains dismal, largely due to the challenges associated with drug delivery to the central nervous system (CNS). The blood-brain barrier (BBB), a highly selective semipermeable border formed by specialized endothelial cells lining the cerebral microvasculature, impedes the passage of most systemically administered therapeutic agents, limiting their efficacy against intracranial malignancies [2]. In recent years, nanotechnology has emerged as a promising avenue to overcome the limitations of conventional

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brain tumor therapies. Nanoparticles, owing to their nanoscale dimensions (typically ranging from 1 to 100 nm) and versatile physicochemical properties, offer unique opportunities for targeted drug delivery, enhanced imaging capabilities, and improved therapeutic outcomes [3]. Among the diverse array of nanomaterials under investigation, peptide-based nanoparticles (PBNPs) have garnered considerable attention due to their biocompatibility, biodegradability, and inherent ability to interact with biological systems [4].

This review presents a comprehensive analysis of recent advancements in the design, synthesis, and application of polymeric-based nanoparticles (PBNPs) for brain tumor diagnosis and treatment. It first outlines the core principles of PBNPs, focusing on fabrication techniques, surface functionalization, and targeting strategies. Additionally, it examines various administration routes, interactions with biological barriers, and mechanisms of cellular internalization.

The review also delves into the array of PBNPs under investigation for theranostic applications in brain tumors, addressing both diagnostic and therapeutic approaches. It critically evaluates the advantages, limitations, and challenges of translating PBNPs into clinical practice. This work aims to serve as a key resource for researchers and clinicians in neuro-oncology, providing a concise yet thorough overview of the current advancements and future potential of PBNPs in brain tumor management.

Brain Tumors

The state of the ordinance, i.e., regulation, is considered crucial when it comes to measuring the steady state of a cell as the health of a cell depends on the health of the environment. Only regulated cells have proper functioning when the cell is misguided, i.e., tumor [1]. explained that brain tumor is simply defined as a tumor in the brain, also known as an intracranial tumor, is an abnormal mass of tissue in which cells grow and multiply uncontrollably [50]. The types of tumors and brain glioblastoma are shown in Figure 1. More than 150 different brain tumors have been reported. This book chapter to a great degree focuses on the recent advances and future outlooks of multifaceted peptide-based nanoparticles for diagnosis of brain tumors.

Nanoparticles

Nanoparticles are materials having size range from 1 to 100nm and are mostly spherical polymeric particles formed from either organic or synthetic polymers. There are different types of nanoparticle carriers as explained in Figure 2. They have a high surface area to volume ratio and are spherical in shape [3]. There are numerous potential uses for these particles. Effective delivery of regional targeting drugs to the brain in neurodegenerative diseases such as Alzheimer and Parkinson remain a challenge due to the restrictive properties of the blood–brain barrier (BBB) which limits the molecular exchange of transcellular transport. Additionally, a healthy BBB effectively shields the brain from exposure to blood-borne nanoparticles. However, it has been demonstrated that several diseases, such as hypertension and allergic encephalomyelitis, increase BBB permeability [5].

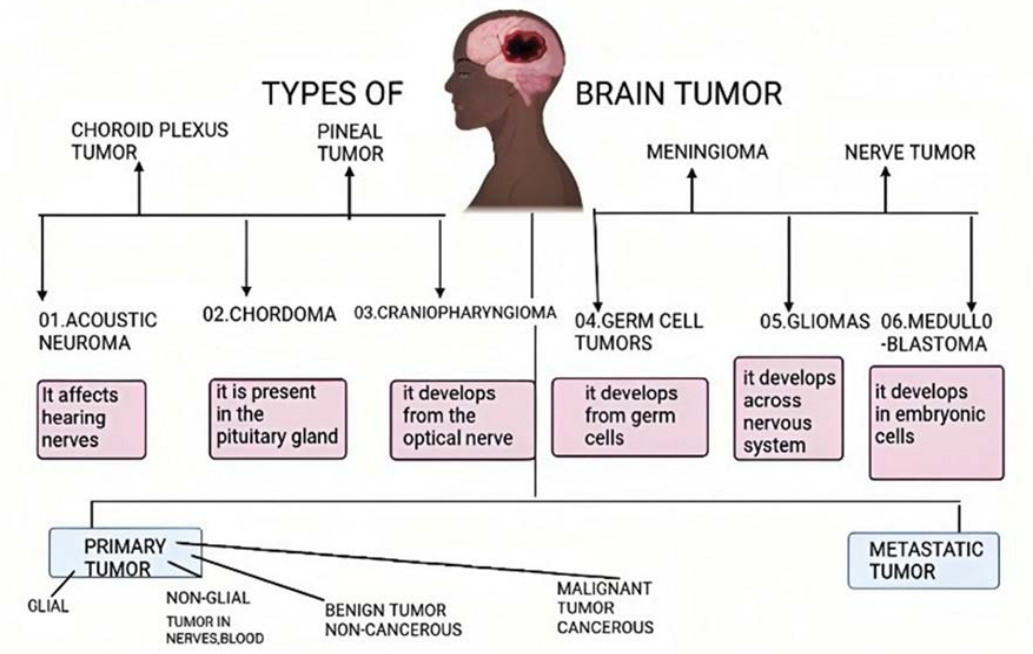

Figure 1: Types of brain tumors.

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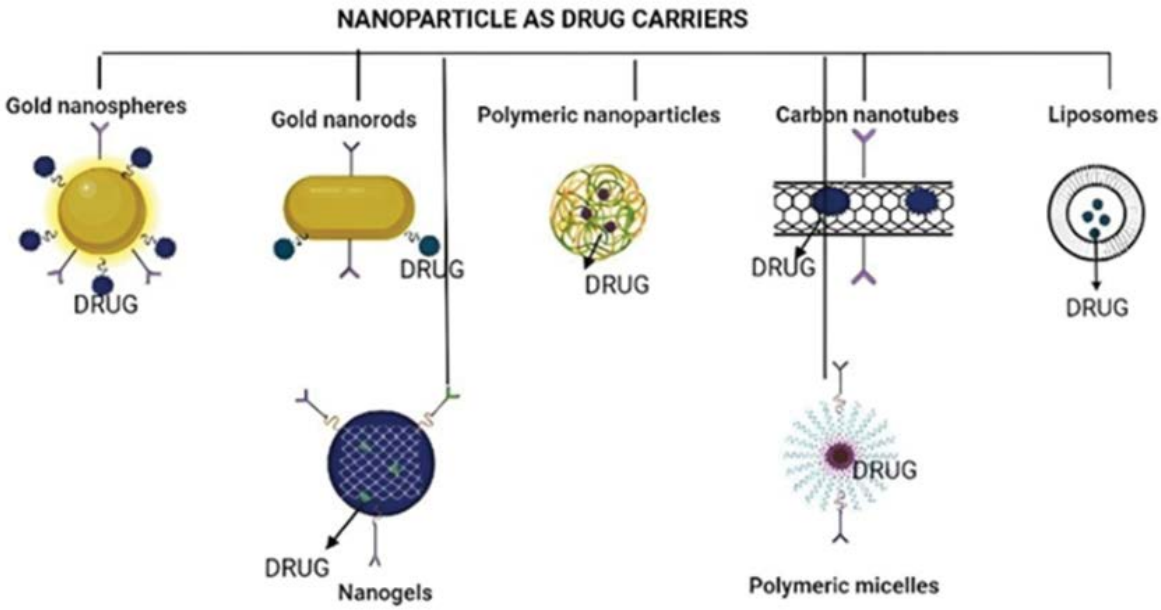

Figure 2: Nanoparticles as drugs.

Peptide-Based Nanoparticles

Peptides consist of amino acids that can self-assemble into variegated nanostructures and show positive biocompatibility and biological activity. Having their deep-rooted benefits, considering functional peptide nanomaterials as multiskilled materials have broad application prospects in the field of material sciences.

I. Solid-phase peptide synthesis techniques allow for molecular modification, resulting in peptide-based nanomaterials with specific characteristics.

II. The addition external chemicals, such as enzymes, to the peptide nanostructure could be used to further functionalize peptide-based nanomaterials.

III. By adjusting the secondary structures of peptide building blocks, such as α-helices and β-sheets, the self-assembly process can possibly be more effectively designed [6].

Fabricating Nanoparticles With Peg

The crucial role of PEGylation in modulating the fate of nanoparticles following intravenous administration is highlighted in Table 1 below. Without PEGylation, nanoparticles are rapidly cleared from circulation due to opsonization and subsequent uptake by phagocytes in the liver and spleen, thereby limiting their therapeutic efficacy [7]. In contrast, PEGylation creates a protective hydrophilic layer on the nanoparticle surface, reducing protein corona formation and minimizing recognition by the immune system [8]. This modification significantly increases the retention time of nanoparticles in the bloodstream, enhancing their ability to reach the target site, including the challenging environment of the brain. By mitigating rapid clearance and promoting prolonged circulation, PEGylation emerges as a key strategy for improving the therapeutic potential of nanoparticle-based drug delivery systems, particularly in the context of brain tumors where crossing the blood-brain barrier is paramount.

Table 1: Comparison between Nanoparticle with PEG and without PEG (PEG= Polyethylene glycol).

Gold nanoparticle without PEG	Functionalized nanoparticle with PEG
• These are designed in a way to elicit absorption of biomolecules for bioimaging and biosensing.	• PEGylation causes passivating effect.
• Nanoparticles are administered intravenously and rapidly removed from circulation.	• This reduces protein corona formation.
• They then accumulate in the liver and spleen.	• The reduced protein corona formation in turn increases the retention time of nanoparticles in the circulatory system.
• Due to opsonization, they are recognized by phagocytes.	• The immune system fails to recognize the nanoparticles.
• Hence, therapeutic efficacy is not shown.	• Hence, therapeutic efficacy is shown

Nanoparticle: Biomedicalapproaches

Nanoparticles demonstrate remarkable potential in diverse biomedical applications, particularly in the realm of brain tumor management. They can be engineered to facilitate targeted drug delivery, overcoming the blood-

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brain barrier (BBB) that often hinders traditional therapies [2]. Additionally, their unique physicochemical properties enable their use as diagnostic tools, enhancing contrast in magnetic resonance imaging (MRI) or aiding in the identification of specific analytes within tissues [3]. Furthermore, nanoparticles hold therapeutic promise, with the ability to directly impact tumor cells, promote tissue repair, and support immunological responses [9]. The rapidly evolving field of nanomedicine is actively advancing the application of nanoparticles, particularly in the treatment of complex diseases such as glioblastoma. This underscores the transformative potential of nanotechnology in revolutionizing healthcare and addressing formidable medical challenges.

Nanoparticles in Therapeutics

Every cell comprises a partition, made of a lipid bi-layer and it's conceded function determines the distinct characteristics of that cell. Keeping track of each cell function helps in identifying the form of conviction. Thus, any therapeutic agent that enters the cell is engineered in such a way it that can provide an efficacious and targeted solution. The accomplishment of nanoparticles comes into sight because of their size which provides an advantage in comparing the size of a cell and therapeutic agent. Nanotechnology could help overcome the clampdown of customary delivery— from massive issuances to that of the biodistribution of barriers at a lower scale, like intracellular trafficking — through cell-specific targeting, and molecular transport to specific organelles [9].

Interaction of Peptides

Peptides interacts with various biological systems types, empowering their utilization in a profusion of scenarios for effective results. According to Zhang et al [10], indicated that peptides have yet to be accustomed in biological systems due to several reasons. The peptide's ability of target binding affinity and accuracy is less than that of proteins. Moreover, they are accessible to protease digestion in biological environments. Their work also mentioned about the short imparting half-lives of peptides which resulted in the requirement for continual administrations to sustain their efficacy. Peptide's function is significantly limited by their ineptitude to perpetuate innate folding structures when secluded from protein, which is an important feature that the PNCs can provide in the form of multi-valency. However, the individual bindings are relatively weak. Their cooperative action allows for robust binding kinetics (mainly due to a significant multivalent binding effect reduction in uncoupling kinetics) based pairs. Interesting examples include delivery of Doxorubicin (DOX) to the nucleus of HeLa cells (Henrietta Lacks, the name of the woman whose cervical cancer cells were used to create the first immortal human cell line in 1951) using mesoporous silica nanoparticles coupled to the Trans-Activator of Transcription peptide (TAT) peptide. Results show that significantly smaller than 50 nm particles were able to carry out TAT peptide-mediated nuclear perception and sustained release of DOX into the nucleus over a 24-h avidity period which can be constructively used for brain tumor therapeutics [11].

Nanoparticles in Theragnostics

The field of nanomedicine offers promising advancements in the diagnosis and treatment of brain tumors, exemplified by the utilization of peptide-based nanoparticles (PBNPs) [4]. These versatile biocompatible carriers can traverse the blood-brain barrier, facilitating targeted drug delivery to tumor sites [2]. Additionally, PBNPs enable enhanced imaging capabilities, aiding in tumor visualization and precise surgical planning [1]. The integration of diagnostic and therapeutic functionalities within a single nanoparticle system, as demonstrated by the use of gadolinium chelates for both imaging and assessing tumor malignancy, exemplifies the concept of theragnostic [9]. Ongoing research and development in this area hold the potential to revolutionize brain tumor management, providing personalized and effective treatment strategies for patients.

Nanoparticle Targeting

Ligands from multiple classifications and categories (chimeras), or multitudinous ligands within the carbon-copy class but with non-identical targets (multi-valency and multi-specificity) have been contrived to refine nanoparticle targeting. It is often inexorable to chemically reform the surface of the nanoparticles with relevant chemistry to establish reactive moieties, dispensing functional groups that can be conjugated to a targeting ligand [7,12]. explained that peptides were conjugated to a variety of nanoparticles, such as metallic NPs like gadolinium oxide, Superparamagnetic Iron Oxide Nanoparticles (SPIONs), Au (gold) NPs, Mesoporous Biocompatible Silica Particles (MBCSPs), micelles and polymers (e.g., chitosan, Poly lactic-co-glycolic acid (PLGA), poly (methyl methacrylate)), and dendrimers, in particular, the short-homing peptide Tet-1, sequence HLNILSTLWKYR, targeted to motor neurons with nanoparticle PLGA (Poly (lactic-co-glycolic acid).

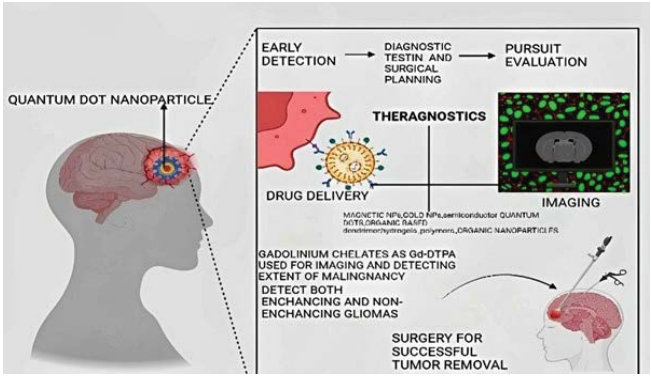

Figure 3: Nanoparticles used in nano-theragnostics.

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Mechanism of Action

Among Target delivery, Cell-Penetrating Peptides (CPPs), Stimuli-Responsive Release, and Immunomodulation are other mechanism of action of peptide-based nanoparticles. CPPs, like Trans activator of transcription peptide (*TAT)* peptides, help nanoparticles cross cellular membranes, delivering drugs directly into the cytoplasm via mechanisms such as endocytosis [13]. This feature is crucial for reaching intracellular targets that are otherwise difficult to access. Additionally, nanoparticles can be programmed to release their cargo in response to specific environmental triggers, such as the low pH or enzymes like matrix metalloproteinases (MMPs) commonly found in tumors, ensuring more precise drug delivery [14]. Peptide-based nanoparticles also play a role in enhancing immune responses by delivering tumor antigens or immunotherapy agents, thereby aiding in tumor recognition and destruction. This immunomodulatory approach leads to more accurate targeting of cancer cells, reducing the risk of broad immune-related side effects [15].

Comparative Analysis

Peptide-based nanoparticles offer distinct benefits compared to traditional diagnostic techniques such as MRI, PET scans, and CT imaging. These nanoparticles are engineered to selectively target cancer cells by recognizing specific markers, which enhances their diagnostic accuracy and improves the localization of imaging agents at tumor sites. In contrast, conventional imaging modalities tend to assess broader regions, which can result in false positives or negatives, ultimately leading to potential misdiagnoses [16]. In addition, peptide-based nanoparticles utilize cell-penetrating peptides that enable the direct delivery of therapeutic agents into cells via endocytosis. This mechanism is particularly effective for accessing intracellular targets that might be difficult to reach with traditional approaches. On the other hand, conventional delivery methods often depend on systemic administration, which can lead to unintended side effects due to the non-specific distribution of drugs [15]. Furthermore, these nanoparticles can be designed for stimuli-responsive release, responding to specific environmental triggers, such as changes in pH or the presence of enzymes in the tumor microenvironment. This feature enhances site-specific drug delivery, minimizing harm to healthy tissues. Traditional diagnostic methods lack such dynamic release capabilities, which can result in less effective therapeutic outcomes [17]. Despite these advantages, peptide-based nanoparticles have their own limitations. Issues such as high production costs, difficulties in scaling, and stability in biological environments must be addressed. Conversely, traditional methods, while well-established, can expose patients to radiation and may not provide the molecular precision necessary for personalized medicine [15].

Routes Of Administration Of Nanoparticle

Three major routes of administration of nanoparticle are explained below in Table 2.

Inhalation Route Treatment And Management Of Chronic Obstructive Pulmonary (Copd)

Pulmonary delivery of nanocomposite microparticles (NCMPs) i.e., PGA-co-PDL nanoparticles with microRNA (miR-146a) by dry powder inhalation [18].

Oral Route of Administration

Sadeghi et al [19] explained that inordinate convenience, high chance of avoidance, efficiency, high patient amenability, decrease in threat traverse infection, and needle contusion are the objectives of why the most popular delivery strategy is oral means.

Transcellular Central Nervous System (Cns) Penetration by Microbes

Microbes that use the transcellular route to get across the BBB, will transverse into the CNS through the endothelial cells. They gain entry to the endothelium of the blood vessel's luminal side and move through the endothelial cells present at that site [20]. Once they have crossed the barrier, these microbes evacuate through the converse side of the cell that is in direct interaction with neurons, microglia, and astrocytes. Absorptive-mediated and receptor-ligand-mediated for transcellular CNS penetration are the 2 recognized methods. Instead of particular ligand-receptor interaction, absorptive-mediated transcytosis (AMT) relies on charge

Table 2: Three major routes of administration (COPD=chronic obstructive pulmonary disease, LPN = Lopinavir).

Inhalation route	Oral route	Transdermal route
ESCAPISM of first-pass hepatic metabolism thus decreasing the dose convolutions.	Food protein nanoparticle using zein and whey protein	It is centred on three foremost layers epidermis, dermis and hypodermis
Peptide (insulin, amylin, chemotherapeutics, interferons and vaccines.	Corn protein zein as a nucleus and whey protein as a crust or framework	a. Intracellular pathway b. Transcellular pathway c. Transappendegal pathway (over hair follicles & sweat glands)
Treatment and management of chronic obstructive pulmonary disease (COPD)	To deliver the antiretroviral drug Lopinavir (LPN) and anticancer agent	Example: liposomes, transferosomes, polymers, nano emulsions.

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exchange. A protein, molecule, or microbe is absorbed into the endothelial cell directly in AMT due to substantial contacts with the endothelium membrane. It is then consigned across the cell and unleashed into the CNS [21].

Brain Barriers

Blood Brain Barrier

The Blood brain barrier is a semi permeable gate which is important for the entry of glucose-like moieties and restrict toxins that can cause core disfigurement to the brain. Microvascular endothelial cells that line the cerebral capillaries penetrate the brain and spinal cord of the higher mammals and other creatures constitute the blood-brain barrier (BBB) with a completely enhanced CNS. It is the largest interface for blood-brain trafficking as the total surface area of a typical adult is presumed to be between 12 and 18 m^2 based on a standard surface area of the micro vessels of 150 and 200 cm^2 per gram of tissue [2].

Brain Cerebrospinal Fluid Barrier

The blood-cerebrospinal fluid barrier (BCSFB), the second barrier, is created by the choroid plexus epithelial cells. The choroid plexus epithelial cells limit the CSF secretion into the ventricular brain system. With several homologous transporters nearby in both tissues, the gesticulation of chemicals from the blood into the CSF is similar in many ways to that of the blood into the brain. According to the studies by Solár et al [22] computably, the blood-brain barrier and the choroid plexus carry substances quite differently. The blood-brain barrier predominates in terms of O2, CO2, glucose, and amino acid entry into the brain. However, the choroid plexus is the prime plot of entry for supplemental compounds. This is the case for Ca^{2+}, where the CSF influx rate constant is tenfold greater than the blood-brain barrier value.

Blood Brain Barrier Route of Administration

The inbuilt protection in the BBB is due to the residence of cerebral endothelium. Three mechanisms that are interceded in nature: receptor-mediated, carrier-mediated, and vesicular transport are the transport contraptions entailed. Most nanosized orders utilize receptor-mediated transcytosis and adsorptive transcytosis [23]. The negatively charged endothelial cells in the cerebrum collaborate with nanoparticles by augmenting positive charges. Nanocarriers comprehending liposomes and solid lipid nanoparticles are known to be potent in decussating the encephalon barricade (BBB). Introductory drug delivered in the brain is of hexapeptide margin (Tyr-D-Ala-Gly-Phe-Leu-Arg), coated with polysorbate 80 nanoparticle. Cell-penetrating peptides like TAT-peptides (derived from HIV) and cationic proteins like albumin are widely used for nanoparticle clamping that accomplishes about the traverse of drugs across the BBB [24]. For example, chitosan-redesigned molecules showed interminable time on the olfactory epithelium. PEG-PLGA nanoparticle coated with lectin having truncated immunogenicity is popularly used as a hauler from the nose to brain delivery [25].

Intravenous Route

The IV route furnishes a prompt response and allows extensive dominance of the contribution of drugs into the body. It is suitable for drugs that cannot be injected into the muscles or other tissues and which cannot be absorbed by the gastrointestinal tract, which also escapes first-pass metabolism [26]. The first-line chemotherapy drug is Paclitaxel which is accessible as a paclitaxel- cremophor (1:1) combination. When Paclitaxel is administered with cholesterol-rich nano emulsion (LDE), had stunted toxicity and showed higher anticancer activity in a mouse model. In solid tumors, LDE tends to concentrate and centralize, which obligates cancer cells in overexpressing LDL receptors [27].

A Brief on Internalisation

Functionalized nanoparticles can recognize the target sites, granted by the small molecules like peptides, aptamers, antibodies etc. as explained by Bahrami, et al [8]. By conjugating onto the surface of the nanoparticles, they then bind to the specific receptors, uniquely expressed by the target cell. Non-covalent interactions, comparatively weaker and unstable in nature than that of covalent bonds accounts for most of the part of conjugation of the CPPs with the cargo/desired molecule compared to covalent bonds. From the mentioned types of different molecules permeating the cargo molecules, the CPPs are generally used in delivering the drugs into sites in need of the delivered compounds, avoiding the major drawbacks of the typical methods of drug formulation and delivery, such as in the case of life-threatening diseases like cancer. PBNP drug delivery systems are of three main categories, based on the peptides at the target site, the CPP involved in the nanoparticle and based on the peptides expressed as the response to the stimuli generated occasionally [28].

Methods of Internalization

Two major pathways of cellular entry are being described by Li et al [4] as, endocytosis (active or energy-dependent uptake) and membrane translocation (direct/passive or energy-independent uptake). Endocytosis follows phagocytic [cell eating] or a pinocytotic [cell drinking] pathway depending on the physio-chemical nature of each nanoparticle. Phagocytic mechanism mostly facilitates the internalization of larger molecules and is performed by leukocytes like neutrophils, dendritic cells, and macrophages as an immune response, while pinocytosis is seen in almost all cells, making it the most popular method of internalization. Ligand-conjugated surface receptors/PEGylated receptors are prone to phagocytosis through adhering to the surface of the target cell through a

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receptor group called 'opsonin receptors' like mannose and scavenger receptors scattered on the surface of the target cells.

The internalization method of a CPP-cargo associates depends on three main parameters, namely - peptide sequence of the CPP, peptide concentration and the lipid content of the host cell membrane. The amino acid sequence by which the CPPs constitute of affects the overall charge of the moiety, which influence it's membrane penetrability. CPP s like TAT and penetrating, owing to their high positive charge gained by electrostatically-associated Arginine and Lysine residues show high permeability than the amphipathic CPPs like MAPs. Concentration of the CPPs is another indispensable parameter which determines the method of nanoparticle uptake to the cell. The higher concentrations of CPPs, or when peptide to cell ratio is higher, energy-independent pathways were encouraged, while at lower concentrations, energy was required. Moreover, the abundance of negatively charged phospholipids and the proteoglycans located throughout the extracellular matrix also showed great effect on the internalization method [29]. Carriers like liposomes (passive or active drug targeting), biodegradable polymers (for localized delivery of bioactive substances) micelles and nanoparticles (carry drugs/nucleic acids) penetrate into the cell and destabilize from within to exert their action [30]. Protein-based nano drugs have shown enhanced efficacy owing to their high specificity, low toxicity and high potency [31]. Cancer cells, characteristically abundant with folate receptors are best targeted by the nanoparticles with folic acid as the targeting ligand, conjugated onto their surface [32].

Macropincocytosis

Macro-pinocytosis is a rapid, receptor-independent uptake involving increased uptake driven by protrusions formed from actin; R8 and TAT with heparan sulfate proteoglycan (HSPG) are necessary for their macro-pinocytic uptake. Clathrin and caveolae-independent endocytosis apart from the above-mentioned pathway, aids in internalizing fluids, membrane components and receptor–ligand complex in animal cells. Selective permeability to components like cholesterols, glycolipids, and lipid raft-associated receptors along with the ligands belongs to the Clathrin and caveolae-independent endocytosis. It is being observed that the caveolae-mediated internalization can occur, even in the absence of caveolae [33].

Classes of Internalization

Nanoparticle surface-receptors could be PEGylated or non-PEGylated, which enhance the target specificity in therapeutics like anti-cancer drugs. Incorporation of CPPs assembled into the hydrophobic nanoparticles as a 'helper' molecule for the large or highly polar molecules to be translocated through hydrophobic membranes. The CPPs show the characteristic spontaneous self-assembly, which achieves the best possible energetic stability through molecular re-shaping. Pinocytosis in case of internalization of small molecules in suspensions like nanoparticles could be further classified as,

- Clathrin or caveolae-mediated endocytosis. 5
- Clathrin/caveolae - independent endocytosis.
- Micropinocytosis.

An Overview of Novel Steps Involved in Internalization

Nanoparticles first interact with the plasma membrane or the extra-cellular matrix from the outside the cell and internalize by endocytosis or any other energy-independent method. Apart from energy-dependent and energy-independent methods so far, novel methods include artificial induction of the internalization like (i)direct injection [gold/silver nanoparticles and imaging agents] intravenously and (ii)genetic material encapsulated with nanoparticle shell in gene therapy is administered inside the body through the veins which is also chosen in real-time toxicity and therapeutic effect monitoring in-vivo. Nanoparticles are functionalized or is subjected to polyethylene glycol [PEG]ation on the surface of the nanoparticles, purposefully incorporated to produce a particular nano-medicine, considering the nature of the cells at the site of interest, and depending on the types of receptors expressed on the cells at the site [8]. As Ruseska et al. [34] mentioned, receptor–ligand interconnection triggers a cascade of actions for the arrangement of actin particles and formation of vesicles which results in invagination of particles inside the cell, followed by the budding and pinching off the cell membrane into the intra-cellular micro-environment Peptide based nanoparticles have an array of physio-chemical properties which facilitate functions deprived by the conventional methods of drug and diagnostics delivery. Enzyme incorporation into nanoparticles facilitates the generation of multimodal therapeutics with synergistic effects to a fixed destination [35].

Role of Epr

Brain comprising of over 100 billion capillaries with several micrometers in diameter, allows passage of drugs easily through the cerebral blood flow. The blood brain barrier in fact with its advanced barricading abilities results in the passive accumulation of drugs in the CNS almost impossible. Enhanced permeability and retention (EPR) effect play a vital role in permitting the active or passive mode of transport through the brain cells in case of brain tumors, which initially causes the new blood vessels formed for the nutrition of the tumors to be formed in a malformed manner [36]. The target site must identify the nanoparticle prior the internalization [37]. The pathway through which

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the cell internalizes remains a question, though it has been over 3 decades since the uprise in nano- therapeutics. In this case, the physio-chemical properties of the CPPs like chain length and charge distribution are considered in developing the drugs, since they determine the mode of entrance [34].

Transversing BBB

The therapeutics designed in treating sites of brain must overcome the blood brain barrier and reach the target site to exert its action. Blood-brain barrier is a protective barrier existing between the brain cells and the blood stream, a protective modification in vertebrate central nervous system. It is a semi- permeable, lipoid layer by which the passage of a multitude of large and small molecules into the microenvironment of the neurons is being regulated. The barrier function is achieved with the help of an array of different transmembrane proteins scattered along the neuronal membrane including mono-carboxylate transporters (MCT1 and MCT2), amino acid transporters, nucleoside & nucleotide transporters, glucose transporter 1 (GLUT1) and ion channels (Na^+/K^+-ATPase pumps). Its activity is achieved in the capillary level and is available on both luminal and ab-luminal surfaces of the blood vessels which carry blood into and out of the brain [36].

Flexible Nature of Nanoparticle in Internalization

Nanoparticles show various methods of internalization, and thus tend to switch between them in favor of the changes in micro-environmental factors. Penetratin, at low concentrations use energy-saving pathways, while at higher concentrations, aid of energy-dependent pathways is sought. Internalization is hence a phenomenon dependent on the features exhibited by the CPP and cell membrane, which decides the subsequent requisites as well as the internalization pathway followed. Li et al. [4] have mentioned that the disruption of micelles could help release the conjugated peptides into the cytoplasm.

Advantages of Peptides in Developing Cpps

The peptide chains in the secondary form are easily manipulated to control self-assembly and hence are preferred in drug delivery systems. Excellent biodegradability and high rate of biocompatibility also qualifies PBNPs for efficient drug delivery and diagnostics. Secondary peptide is established by the presence of hydrophobic patches on one surface and positive/negative charge or polar nature on the other surface of alpha-helices [MPG, Penetratin, pVec etc.] while alternative pleats with hydrophobicity and hydrophilicity of beta-sheets is being exposed to the hydrophilic solvents [highly-prolinated peptides]. In fact, the non-amphipathic class of CPPs, abundant with positively charged amino acids show greater permeability through the cytoplasm. CPPs based on the charge overall forms peptides of cationic nature due to the presence of arginine and lysine, amphipathic peptides comprised mostly of hydrophobic residues like alanine, methionine and valine and amphipathic peptides made of both hydrophilic and hydrophobic residues. Hence the permeability of cationic peptides could be increased by involving more arginine molecules. Also, at least four helical turns in alpha helices tend to enhance the permeability. The hydrophobic fragments of some peptides showing affinity towards the hydrophobic portion in the cell membranes play a vital role in the cellular internalization mechanism. Peptide based nanoparticles also exhibit excellent thermostability, mechanical stability, semi-conductivity. Hence, self-assembly structures composed of short peptides may also possess semiconducting properties [34]. Functionalization accounts for the conjugation of the CPP molecules with the desired nano-molecules. The drug formulation targeting the brain should be able to overcome the blood brain barrier and to reach the region of interest.

Self Assembly of The Peptide Nanoparticle

Self-assembly of peptides can be termed as aggregation of molecules by non-covalent forces (electrostatic interactions, hydrogen bonding, van der Waals forces and hydrophobic forces) with a specific order of arrangement, using molecular recognition either between the molecules or between fragments of molecules [38]. Factors affecting self-assembly of nanoparticle plays a crucial role in understanding its nature which is explained in Table 3. These interactions allow peptide aggregates to form specific and ordered nanostructures [12]. This process is spontaneous and is carried out by thermodynamics and chemical kinetics. The self-assembly of peptides is affected by the external environment, which includes factors such as solvents, pH, enzymes, ion concentration, temperature, etc.

Self-assembled peptide nanomaterials can undergo various modifications such as nanoparticles, nanofibers, micelles, hydrogels, nanotubes etc. Types of self-assembly nanoparticle are explained in Figure 4.a). These modifications are due to the favorable properties of these nanomaterials such as designability and adjustment to physicochemical parameters. Advantages of using self-assembled peptide nanostructures are primarily by improving the bioavailability of the active ingredient of the carrying drugs, which would lead to higher effectiveness [42].

The Brain's Pharmacological Transporters, Peptides

Receptor Targeted Peptides

The delivery of therapeutic agents to the brain is carried out by a class of proteins called as receptor targeted peptides, which are designed to interact with specific receptors in the brain. These receptors are mainly of three types, namely:

1. Transferrin receptor (TfR)
2. Low-density lipoprotein family receptors (LDLR) and
3. Nicotinic acetylcholine receptor (nAchR).

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Out of these, transferrin receptors are abundant in brain capillary endothelial cells [43]. Figure 4.b) below shows the classification of cell penetrating peptides (CPPs).

Shorter chains of peptides can cross the membrane barrier with relative ease due to their characteristic properties. Some can pass the blood-brain barrier and deliver to subcellular compartments [43]. Several characters affect CPPs such as structure, concentration, length, and charge. When CPPs are associated together with nanomaterials, bioavailability, stability, selectivity, and in vivo efficiency are promoted [44]. Peptides such as chlorotoxin and F3 can be attached to nanoparticle surface to target nanoparticle-based MRI contrast agents to tumors [45]. Intravenous injection of iron oxide containing F3- targeted nanoparticles demonstrated implanted tumor's sustained contrast enhancement and was found to be more constant than their identical non-targeted

Table 3: Factors affecting self-assembly of peptides.

Factors affecting	Condition present	Effect	Reference
pH	1. pH=5 2. pH=6and7 3. pH>7	1.Spherical micelle formation. 2.Nano-fiber formation. 3.Longer nano-fibers formed	**[16]**
Temperature	Initially on increasing	1. Exists as monomers 2. Formation of nanofibrils, micelles and other nanostructures like diphenylalanine peptides, elastin-like peptides (ELPs), etc. occurs as a result.	**[39]**
Enzymes	Suitable enzyme	Hydrophobic compounds, hydrogels and hydrophobic nano-materials formed.	**[6]**
Ion concentration	Salt-ions	1. Shielding of charged groups. 2. Weaker electrostatic interactions between molecules. 3. Inter-molecular hydrophobic bonding forces are increased. 4. Makes the peptide molecules more prone to polymerization. 5. Leading to self-assembly.	**[40]**
Solvent	Suitable solvent	1. Alters morphology of the peptide. 2. Leads to chiral inversion.	**[41]**

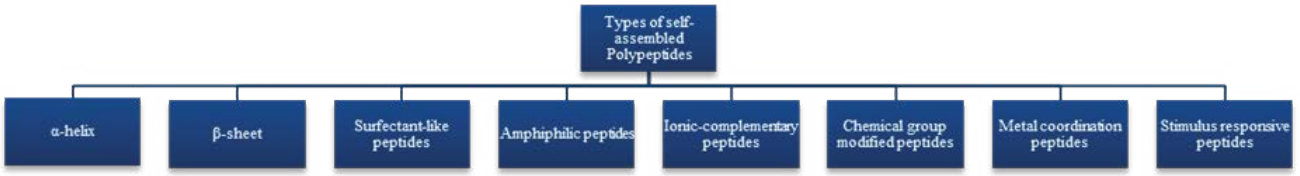

Figure 4a

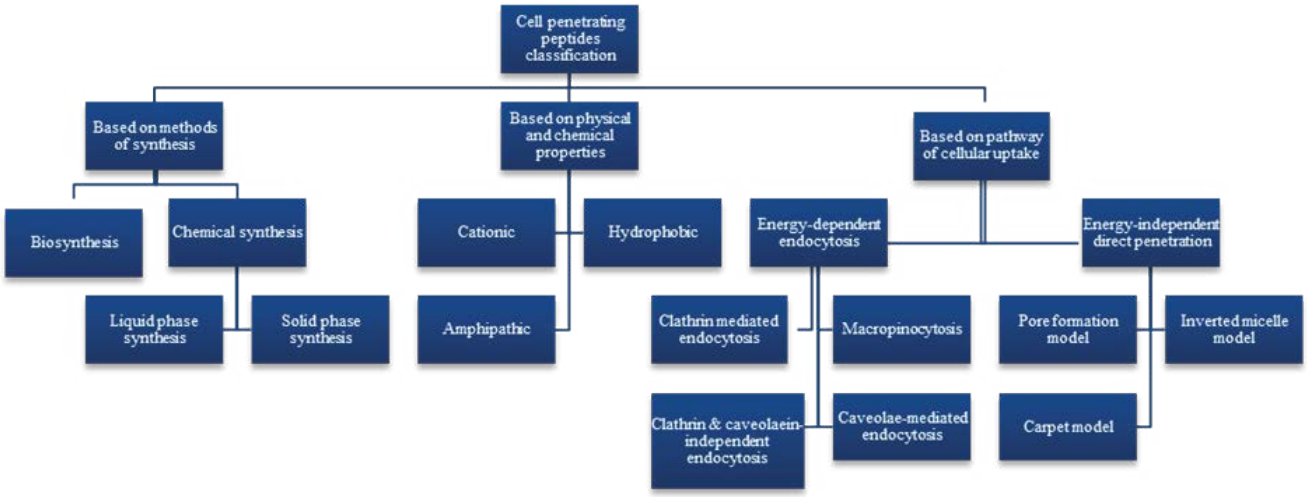

Figure 4b

Citation: Soumya V Menon, Abira R, Shyam Gokarn, Nekath Gamlath Raalalage Hasanjana Rashari Senevirathne, Chaqshu Tandin Bidha, Asha Kademane. Multifaceted Peptide Based Nanoparticles for Diagnosis of Brain Tumors: Recent Advances and Future Outlooks. Journal of Biotechnology and Biomedicine. 8 (2025): 59-71.

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nanoparticle counterparts [46]. Targeting peptides can induce nanoparticle preservation or binding to their target cells. Understanding partially observed cures' effect on peptide function is explained in Figure 4.c) Poly (α-L-glutamic acid) (α-PGA) are a form of covalent drug delivery system which have been reported by Julia et al [47] for the delivery of chemotherapeutics such as Paclitaxel (TXL), Camptothecin, Doxorubicin, etc.

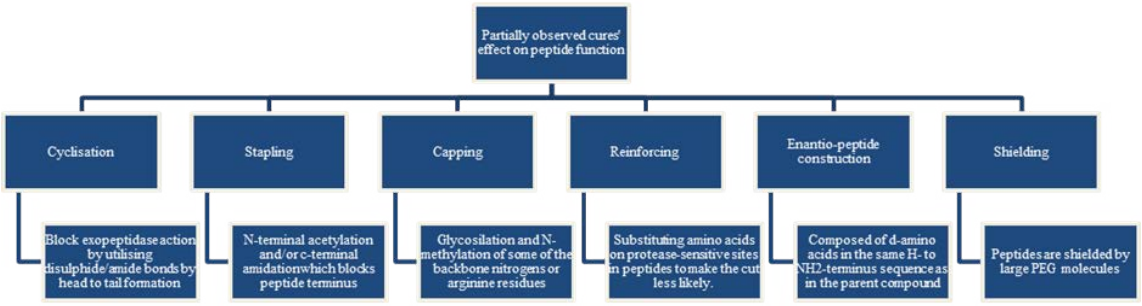

Figure 4c:

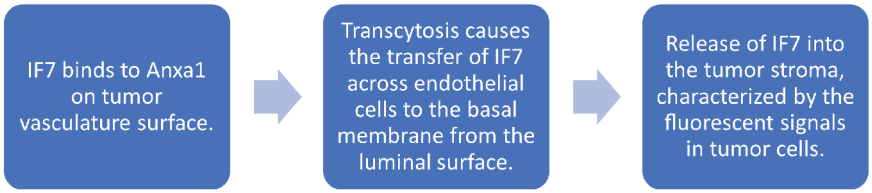

Figure 5: Crossing blood brain barrier and delivering drug to the brain stroma (ANXA 1 = Annexin A1 binding peptide, IF7 = Tyr-D-Ala-Gly-Phe-Leu-Arg hexapeptide). – Section 18.1.

Case Study

Annexin A1-Binding Peptide Overcomes The Blood-Brain Barrier To Target Brain Tumors

It is on the on the tumor vasculature surface that the Annexin A1 is expressed. When the hexapeptide IF7 is injected intravenously, it targets tumor vasculature via annexin A1 (peptide identified and designated as Anxa1). According to reports, IF7 overcomes the blood-brain barrier. Intravenously injected IF7C(RR)-SN38 was found to eradicate mouse brain tumors. On Anxa1 protein, IF7 binds sufficiently with the first 15 amino acid residues **[48]**. Some of the ways in which IF7 can cross the BBB and deliver drug to the brain stroma is shown in **Figure 5** below:

Nanotechnology Applications For Glioblastoma

Glioblastoma exhibits aggressive characteristics as there is frequent dysregulation of its phospholipid signaling [10]. Phosphoinositide 3-Kinase (PI3K) hyperactivation plays an important role in tumorigenesis and metastasis, thus Receptor Tyrosine Kinases (RTK), PI3K signaling pathways are emerging as upcoming targets for glioblastoma therapy [49]. Nanoparticles are also targeted to brain tumor cells by larger peptides such as cytokines and monoclonal antibodies. Till now, considering both in vitro and in vivo, 3 peptides have been reported which are capable of targeting nanoparticles on surface of expressed glioma cells. By means of phage display techniques, two of the peptides, Arginine-Glycine-Aspartic Acid (RGD) and the peptide F3 which is a sequence derived from tissue factor pathway inhibitor (TFPI)-3, were discovered for their capacity to target cell surface markers on angiogenic epithelium in implanted tumors [45]. F3 is a 31 amino acid residue which binds to nucleolin (cell surface receptor capable of expressing in proliferating angiogenic and tumor cells. Nano-cyan is a methylene blue-loaded polyacrylamide nanoparticle, whose surface is coated with numerous F3 targeting peptides and a coating of cysteine (to prevent non-specific binding). Deep staining of 9Lgliosarcoma cells with nano-cyan was demonstrated in an F3-dependent manner, which marked for the first published report of application of nanoparticle in staining tissues under normal lighting conditions.

Future Outlook

The current advancements in PBNPs for brain tumor theranostics demonstrate significant potential; however, several critical areas remain to be explored. Future research must prioritize enhancing the specificity and therapeutic efficacy of PBNPs through novel surface modifications and targeted delivery strategies. Addressing the challenges of PBNP degradation, endosomal escape, and potential long-term toxicity will be paramount to ensuring their successful clinical translation. Furthermore, the development of multifunctional PBNPs capable of co-delivering therapeutic

agents or integrating diagnostic and therapeutic functionalities within a single platform ("theragnostic" PBNPs) presents a promising direction for future investigation.

Equally important will be the creation of more sophisticated in vitro and in vivo models that accurately replicate the complex tumor microenvironment, enabling a more thorough evaluation of PBNP safety and efficacy prior to clinical application. Continued research into the long-term effects of nanoparticle exposure is vital to ensure safety and minimize any potential risks to human health.

In view of the above, PBNPs have emerged as a powerful tool in the management of brain tumors, offering significant advancements in diagnosis, targeted therapy, and personalized treatment. While notable progress has been achieved, sustained research efforts are critical to fully unlocking the potential of PBNPs in neuro-oncology and advancing their successful transition to clinical practice.

Conclusion and Future Challenges

Receptor targeted peptides are rapidly degraded by proteases and are refrained by the blood-brain barrier. Peptide molecules usually face a challenge of easily disassembling in enzymatic activity and having low efficiency in drug loading and release in the target site comprising of complex physiological environment. When peptides are conjugated, they might possess new properties which can be different from the parent peptide itself. Peptides are also reported to cause antigenicity with responses such as IgG and IgM antibodies, cytokine release, and complement activation which may result in anaphylaxis. Hemolytic potential may be one of the most significant sources of toxicity in some peptides. The presence of peptidases in the digestive system causes rapid degradation of peptides composed wholly of natural amino acids, eventually causing lower effectiveness.

Peptide-based nanoparticles hold considerable promise for a variety of clinical applications, especially in areas like targeted cancer therapy, gene therapy, and personalized medicine. Peptides that self-assemble based on their responses to ion concentration have an extensive range of potential applications in the field of medicine. Usually, drugs need to be administered at their maximum tolerable dosage when targeting the brain as they often rely in passive diffusion. Hence, they have a possibility of causing adverse side effects in the body. Their capacity to deliver therapeutic agents directly to targeted cells enhances treatment effectiveness while reducing adverse effects. Future investigations should aim at refining nanoparticle designs to boost their targeting and delivery efficiency, potentially leveraging artificial intelligence to better predict their interactions with biological systems. This could result in multifunctional nanoparticles that are capable of co-delivering imaging agents alongside therapeutics, thereby allowing for real-time monitoring of treatment responses. In the case of cell penetrating peptides, there are several areas which need to be worked on. CPPs are not very specific in their selectivity towards a particular membrane or receptor. They are less likely to escape from the endosome and eventually may get trapped, thus affecting the intracellular delivery of endocytosed agents. Several iron oxide nanoparticles targeted with peptides are currently being investigated in preclinical research and show promise as tumor-specific contrast agents. Easily detected neoplastic tissue by radiography is sometimes indistinguishable from normal brain tissue. In several cases, especially in diffusely invasive brain tumors, it is observed that residual tumor is left behind after gross total resection. Existing areas of improvement for researchers include staining particularly tumor cells, concentrating adequate amount of dye within tumor cells to achieve contrast and lastly creating a dye useful for broad spectrum use of tumors.

Nanoparticles may be able to serve as the means through which drugs can pass across the blood-brain barrier and the blood-tumor barrier which will be able to efficiently deliver drug at its therapeutic levels. Once nanoparticles enter the systemic circulation, they are usually cleared by the reticuloendothelial system via opsonization, phagocytosis (by macrophages) and finally their uptake by liver and spleen. Given the slow rate at which bile neutralizes nanoparticles, residual nanoparticles may pose potential long-term risks. Therefore, further research is essential to fully understand the extended health implications of nanoparticle exposure. Nonetheless, several challenges must be addressed to fully realize the potential of peptide-based nanoparticles in clinical settings. Issues such as the scalability of production, their stability under physiological conditions, and the establishment of clear regulatory guidelines are critical. The high costs and complexity associated with current manufacturing processes may limit their widespread use, and rigorous testing protocols will be necessary to ensure safety and efficacy. Overcoming these challenges will require strong collaboration among researchers, clinicians, and regulatory bodies to effectively advance the application of peptide-based nanotechnology in medicine.

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