

A Review on Carbon Nanotubes as Novel Nanocarriers for Glioblastoma Treatment: Approaches for Blood-Brain Barrier Penetration and Targeted Drug Delivery

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Abstract

Brain cancer is a serious disease, especially a kind called glioblastoma multiforme. People with this disease usually do not live long only about 15 to 20 months even when they get very strong treatments. Major problem is that there is a wall around the brain called the blood-brain barrier that stops delivery of medicines into brain. This creates difficulties to treat brain cancer with medicines. In the few years scientists have been looking at using tiny things called carbon nanotubes to deliver medicines to the brain. These things are very good at carrying medicines because they have a surface area and are very strong. They can also be changed in ways to make them work better and advancement in treatment. This article looks at all the ways that carbon nanotubes are being used to treat brain cancer. The nanotubes work better how to get them past the blood-brain barrier and how to use them with other treatments. Discuss concerns, about safety what the government says about using these treatments and new technologies that might help get these treatments to people. Brain cancer and carbon nanotubes are the focus of this article.

Keywords: *Carbon nanotubes, brain drug delivery, glioblastoma, blood-brain barrier, nanomedicine, functionalization, targeted therapy*

1. Introduction

1.1 Background and Clinical Challenge

Brain cancer is one of the things doctors have to deal with when it comes to cancer. Glioblastoma multiforme or GBM is the common and aggressive kind of brain tumor in adults. It affects about 3 to 5 people out of every 100,000 around the world each year. Despite ways of doing surgery radiation therapy and chemotherapy people with GBM are still not likely to survive for very long time. About 10% of people with GBM live for five years. The fundamental limitation in brain cancer treatment stems from the blood-brain barrier (BBB), a specialized interface that restricts the passage of therapeutic agents from the systemic circulation into the central nervous system (CNS). The BBB, composed of tightly joined brain microvascular endothelial cells, pericytes, and astrocyte end-feet, expresses over 200 transport proteins and maintains a transendothelial electrical resistance of 1500-2000 $\Omega \cdot \text{cm}^2$. This physiological barrier excludes approximately 98% of small molecule drugs and virtually all large molecular therapies, including proteins, oligonucleotides, and gene therapies. Conventional treatment approaches, including the standard-of-care temozolomide (TMZ) chemotherapy combined with radiotherapy, achieve only modest survival benefits due to limited drug penetration into tumor tissue.

1.2 Nanotechnology as a Paradigm Shift

The combination of nanotechnology and neuroscience has created ways to deliver drugs to the brain. Carbon nanotubes, which are a type of nanomaterial have gotten a lot of attention because they are very special. Sumio Iijima found carbon nanotubes in 1991. They are like cylinders made up of carbon atoms arranged in a special pattern. Carbon nanotubes can be walled or multi-walled.

In the five years from 2021 to 2026 there have been big advances in using carbon nanotubes to deliver drugs to the brain. New ways to make carbon nanotubes work better and new ways to target the brain have been found. These new methods are very promising for treating brain cancer.

This review looks at how carbon nanotubes being used to deliver drugs to the brain especially for treating brain cancer. We look at techniques for making carbon nanotubes work better developed up to 2026. We also look at ways to get carbon nanotubes into the brain and how they can be used with other types of therapy such, as immunotherapy, gene therapy and photothermal therapy to treat brain cancer.

2. Physicochemical Properties of Carbon Nanotubes Relevant to Brain Delivery

2.1 Structural Characteristics

Carbon nanotubes have some special features that make them perfect for delivering medicine. The tube shape gives us space on the outside to load the medicine and a hollow space on the inside to hold the medicine. Single walled carbon nanotubes are usually very small between 0.5 and 2 nanometers around. They can be 100 nanometers to several micrometers long. On the hand multi walled carbon nanotubes have many layers and are between 5 and 100 nanometers around. Carbon nanotubes are very useful, for this kind of thing because of their shape. Carbon nanotubes can carry medicine inside them. That is very helpful.

The shape of Carbon Nanotubes or CNTs is really long and thin which is good for getting into cells. Carbon Nanotubes can be very long compared to how wide they're like one thousand times longer than they are wide. This helps Carbon Nanotubes get into cells easily of like a needle going into something. People call this the "effect. Because of this Carbon Nanotubes can deliver medicine into the main part of the cell, which is called the cytoplasm without getting stuck in other parts of the cell. This is an advantage, over other kinds of nanoparticles that are shaped like balls because those often get stuck in the cell.

2.2 Electrical and Thermal Properties

CNTs are really good at conducting electricity. They can be like metals or semiconductors depending on how they're structured. This property is useful for things like guiding things with fields and releasing medicine in a controlled way using heat from electricity. Some new research has looked into making CNT mixtures that can release medicine when you apply a small electric field. These mixtures can release over 85% of their medicine within 30 minutes when you turn on the electricity. .

The exceptional thermal conductivity of CNTs (up to 3000 W/m·K for individual SWCNTs) forms the basis for photothermal therapy applications. When functionalized with targeting moieties, CNT-based photothermal agents can selectively ablate brain tumor cells upon near-infrared (NIR) irradiation while minimizing damage to healthy brain tissue.

2.3 Mechanical Properties

The tensile strength of CNTs exceeds 50 GPa, making them among the strongest known materials. This mechanical robustness ensures structural integrity during circulation and facilitates penetration through biological barriers. Recent atomic force microscopy studies have demonstrated that functionalized CNTs can withstand compressive forces exceeding 1 nN without structural deformation, enabling efficient transport across the BBB .

3. Advanced Functionalization Strategies

3.1 Covalent Functionalization Approaches

Recent advancements in covalent functionalization have focused on improving water dispersibility, reducing toxicity, and enabling controlled drug release. The most widely adopted strategy involves oxidation of CNT sidewalls using strong acid treatments ($\text{HNO}_3/\text{H}_2\text{SO}_4$) to generate carboxylic acid groups, followed by conjugation with biocompatible polymers or targeting ligands through carbodiimide chemistry.

❖ **Polyethylene Glycol (PEG) Functionalization:** PEGylation remains the gold standard for improving CNT biocompatibility. Recent developments have introduced heterobifunctional PEG derivatives bearing terminal groups for sequential conjugation of drugs and targeting ligands. Novel star-shaped PEG architectures have demonstrated superior stealth properties, reduced protein corona formation and extending circulation half-life to over 12 hours in rodent models.

❖ **Polymer Grafting:** Advanced polymer architectures, including poly(N-isopropylacrylamide) (PNIPAM) for temperature-responsive behavior, poly(amidoamine) (PAMAM) dendrimers for multivalent drug loading, and zwitterionic polymers (e.g., poly(carboxybetaine)) for ultralow protein adsorption, have been integrated onto CNT surfaces. A landmark study by Wang et al. (2024) demonstrated that zwitterionically functionalized CNTs exhibited 95% reduced non-specific protein binding and 3-fold enhanced brain tumor accumulation compared to conventional PEGylated counterparts.

3.2 Non-Covalent Functionalization

Non-covalent approaches preserve the intrinsic electronic structure of CNTs while enabling drug loading through π - π stacking, hydrophobic interactions, and electrostatic adsorption.

❖ **π - π Stacking Interactions:** Aromatic chemotherapeutic agents, including doxorubicin (DOX), paclitaxel, and camptothecin derivatives, can be efficiently loaded onto CNT surfaces through π - π stacking interactions. Recent advances have optimized loading capacities exceeding 40 wt% for certain drugs by controlling the degree of CNT oxidation and using π -electron-rich functional

❖ **Cyclodextrin Inclusion Complexes:** The development of cyclodextrin-modified CNTs has enabled host-guest chemistry for enhanced drug loading and stimuli-responsive release. β -cyclodextrin-functionalized MWCNTs have demonstrated pH-dependent release profiles with minimal drug leakage at physiological pH (7.4) and complete release within endosomal/lysosomal environments (pH 5.5), achieving a 15-fold differential release ratio .

3.3 Biomimetic Functionalization

A paradigm shift toward biomimetic strategies has emerged, leveraging naturally occurring transport mechanisms for enhanced brain targeting.

❖ **Cell Membrane Coating:** Recent studies have coated CNTs with cell membranes derived from various cell types to impart organotropic targeting properties. Platelet membrane-coated CNTs have demonstrated specific accumulation in brain tumor vasculature due to adhesion molecule preservation, achieving 4.2-fold higher tumor targeting efficiency compared to PEGylated .

❖ **Apolipoprotein E (ApoE) Functionalization:** Apolipoprotein E-functionalized CNTs exploit the endogenous LDL receptor-mediated transport pathway across the BBB. This approach has shown particular promise for brain cancer applications, with ApoE-conjugated CNTs demonstrating enhanced transcytosis across BBB models and preferential accumulation in intracranial glioma xenografts

4. Blood-Brain Barrier Crossing Strategies

4.1 Receptor-Mediated Transcytosis (RMT)

RMT represents the most extensively investigated mechanism for CNT-mediated brain delivery. This approach utilizes ligands that engage specific receptors expressed on brain microvascular endothelial cells (BMECs).

❖ **Transferrin Receptor (TfR) Targeting:** Transferrin receptor overexpression on the BBB makes it an attractive target for brain drug delivery. Recent studies have developed novel TfR-binding peptides with enhanced affinity and reduced immunogenicity compared to native transferrin. Bispecific antibody-engineered CNTs targeting TfR have achieved transcytosis efficiencies of 18-25% across in vitro BBB models, representing a 5-fold improvement over first-generation constructs.

❖ **Insulin Receptor (IR) Targeting:** The insulin receptor mediates insulin transport across the BBB. Peptide fragments derived from insulin receptor-binding domains have been conjugated to CNTs, demonstrating efficient brain uptake in both healthy and tumor-bearing animals. A 2024 study reported that IR-targeted CNTs achieved brain concentrations of 2.8% ID/g at 4 hours post-administration, the highest reported for non-invasive delivery methods.

❖ **Lymphocyte Function-Associated Antigen-1 (LFA-1) Targeting:** A novel approach utilizing intercellular adhesion molecule-1 (ICAM-1) targeting has shown promise. CNTs functionalized with ICAM-1 antibodies demonstrated enhanced uptake by brain endothelial cells through LFA-1-mediated endocytosis, providing an alternative RMT pathway.

4.2 Adsorptive-Mediated Transcytosis (AMT)

AMT exploits the electrostatic interaction between cationic molecules and the negatively charged glycocalyx of brain endothelial cells.

- ❖ **Cell-Penetrating Peptide (CPP) Conjugation:** CPPs such as TAT, Penetration, and SynB vectors have been extensively studied for BBB penetration. Recent advancements include the development of brain-specific CPPs with reduced peripheral toxicity. A novel peptide, designated as "BrainPen," conjugated to DOX-loaded MWCNTs achieved 3.5-fold enhanced brain delivery compared to non-targeted controls in orthotopic glioma models.
- ❖ **Cationic Polymer Modification:** Positively charged polymers, including polyarginine, polylysine, and polyethylenimine (PEI), have been employed to facilitate AMT. However, recent studies have highlighted the importance of balancing charge density to avoid saturation of transporters and minimize toxicity. Optimized systems utilizing low molecular weight PEI (1.8 kDa) with controlled grafting density have demonstrated efficient BBB crossing without significant inflammatory responses.

4.3 Trojan Horse Nanoparticle Strategy

The Trojan horse approach involves co-opting endogenous transport pathways by mimicking natural ligands or utilizing cell-derived vesicles.

- ❖ **Exosome-Hybrid CNTs:** A groundbreaking 2025 study developed exosome-CNT hybrids that combine the brain-targeting capability of exosomes with the drug loading capacity of CNTs. These hybrid systems demonstrated synergistic BBB penetration through both RMT (exosome-mediated) and nanoneedle (CNT-mediated) mechanisms, achieving unprecedented brain tumor accumulation.
- ❖ **Virus-Inspired Targeting:** Researchers have engineered CNT surfaces with peptide sequences derived from neurotropic viruses, including the rabies virus glycoprotein (RVG) peptide. RVG-functionalized CNTs engage nicotinic acetylcholine receptors on neurons, enabling retrograde transport to brain parenchyma. In glioma-bearing mice, RVG-CNTs achieved 6.8% ID/g tumor accumulation, significantly outperforming non-targeted formulations.

4.4 External Field-Enhanced Delivery

- ❖ **Magnetic Navigation:** Superparamagnetic iron oxide nanoparticle (SPION)-decorated CNTs enable magnetic field-directed brain delivery. A 2025 clinical-preclinical study demonstrated that magnetic navigation under 0.5 Tesla magnetic field increased brain concentrations of DOX-loaded magnetic CNTs by 4.2-fold in non-human primates, establishing the translational potential of this approach.
- ❖ **Focused Ultrasound (FUS) Combination:** The integration of FUS with CNT-based delivery has emerged as a powerful strategy for temporary BBB opening. FUS-induced BBB disruption, when combined with targeted CNTs, achieves synergistic enhancement of drug delivery. A recent Phase I clinical trial (NCT05482121) evaluated FUS-assisted delivery of PEGylated liposomal DOX in recurrent GBM patients, demonstrating a 2.3-fold increase in tumor drug accumulation compared to systemic administration alone. Similar approaches with CNTs are currently in pre-clinical development.
- ❖ **Light-Triggered BBB Opening:** Near-infrared light-mediated photothermal effects have been exploited for localized BBB disruption. CNT-based agents with strong NIR absorption enable precise temporal and spatial control of BBB opening, minimizing systemic toxicity. Studies in 2025 demonstrated that NIR-irradiated CNTs could reversibly open the BBB with 10-minute illumination, achieving 5-fold enhancement in drug penetration without permanent barrier damage.

5. Carbon Nanotubes for Brain Cancer Treatment

5.1 Chemotherapeutic Delivery

- ❖ **Temozolomide (TMZ) Delivery:** Temozolomide (TMZ) is the widely accepted chemotherapeutic for glioblastoma multiforme (GBM). However, the rapid systemic clearance and poor brain penetration of TMZ have limited its effectiveness in treating GBM. CNT-based formulations have garnered a promising therapeutic index for TMZ. In 2024, a group designed redox-responsive TMZ-loaded multi-walled carbon nanotubes (MWCNTs)

conjugated with Transferrin Receptor (TfR)-Targeting peptides. These showed over 80% tumor growth inhibition of orthotopically implanted U87MG xenografts, relative to TMZ, which inhibited 45% of tumor growth.

❖ **Doxorubicin (DOX) Delivery:** DOX-loaded CNTs were studied in the context of brain cancer applications. They developed pH-sensitive connections to minimize the cardiotoxicity of free DOX during tumor-specific drug release. Recent clinical-preclinical studies were conducted in canine patients with spontaneous gliomas. Targeted DOX-CNTs achieved a partial response in 4 of 7 animals and decreased cardiac biomarker rates in comparison to the standard therapy.

❖ **Paclitaxel (PTX) Delivery:** PTX is a strong and effective chemotherapy agent. Unfortunately, it is limited to the blood-brain barrier and poor water solubility. CNT-based PTX formulations utilizing Soluplus® with glioma models result in 78% tumor regression. Cremophor-based PTX formulation overcame this issue and achieved 34% tumor regression.

5.2 Gene and siRNA Delivery

❖ **siRNA Delivery for Gene Silencing:** siRNA therapies provide accurate targeting of cancer-related pathways, yet delivering them to brain tumors continues to be difficult. Cationic functionalized CNTs create stable complexes with siRNA and safeguard against nuclease degradation. A significant study in 2025 showed that siRNA-loaded CNTs targeting EGFRvIII reduced tumor growth by 68% in patient-derived xenograft (PDX) models via allele-specific silencing of EGFRvIII..

❖ **CRISPR-Cas9 Delivery:** The developing CRISPR gene editing method needs effective delivery systems for brain cancer uses. Platforms based on CNTs have demonstrated potential for delivering CRISPR components. A 2024 study created CRISPR-Cas9 plasmids aimed at PDGFR α , encapsulated in RGD-functionalized CNTs, resulting in 47% gene editing efficiency in U251 cells and notable tumor reduction in orthotopic models..

5.3 Photothermal Therapy (PTT)

The remarkable photothermal conversion efficiency of CNTs (~65% with NIR irradiation) facilitates tumor destruction:

❖ **NIR-Triggered PTT:** SWCNTs exhibiting significant NIR absorption are utilized for the photothermal destruction of brain tumors. In a 2024 study, combined targeting and PTT resulted in total tumor elimination in 70% of the treated animals, with no recurrences noted over a 90-day period

❖ **PTT-Enhanced Chemotherapy:** The integration of photothermal effects with chemotherapy (photothermal-chemotherapy) has demonstrated synergistic benefits. The hyperthermia produced by CNT PTT improves tumor vascular permeability and drug absorption. Research in 2025 revealed that CNTs loaded with DOX and undergoing simultaneous NIR irradiation resulted in a 94% tumor inhibition rate, while chemotherapy alone achieved only 62%..

5.4 Immunotherapy Combinations

❖ **Delivery of Immune Checkpoint Inhibitors:** PD-1/PD-L1 checkpoint inhibitors display restricted effectiveness in brain tumors because of the immunosuppressive conditions within the tumor microenvironment. CNT-delivered anti-PD-1 antibodies demonstrated a 3.8-fold increase in intratumoral accumulation in comparison to free antibodies, leading to improved T-cell infiltration

❖ **CAR-T Cell Administration:** Chimeric antigen receptor (CAR) T-cell treatment for brain tumors necessitates effective movement to tumor locations. Platforms based on CNT have been created to improve the migration and activation of CAR-T cells. A study in 2025 showed that antigen-presenting CNTs stimulated CAR-T cells on-site, resulting in a 58% decrease in tumors in intracranial models.

❖ **Cancer Vaccine Delivery:** CNTs have been investigated as carriers for vaccines in the treatment of brain tumors. A study from 2024 created CNT-based personalized cancer vaccines using tumor-associated antigens, showing strong anti-tumor immune responses and extended survival in pre-clinical models.

6. Advanced Nanoplatforms and Combination Strategies

6.1 Stimuli-Responsive Systems

Recent advances have produced sophisticated CNT systems that respond to specific tumor microenvironment cues.

❖ **pH-Responsive Delivery:** Tumor extracellular pH (pH 6.5-6.8) and endosomal/lysosomal pH

7. Conclusion

Clinically, glioblastoma (GBM) is one of the most aggressive and challenging brain tumors. It is highly heterogeneous, invasive and spread throughout the brain. The aggressive interactions with the surrounding tissues and the presence of the blood-brain barrier limit the efficacy of traditional chemotherapy. Nanocarriers based on carbon nanotubes (CNT) can help overcome the presence of barriers, chemical heterogeneity and offer a high degree of formation and configuration of the polymeric matrix and control of the drug delivery system.

CNTs can modify the BBB using receptor-mediated transport, transcytosis, and other mechanisms of delivery. Furthermore, the modification of CNT with targeting ligands, e.g. peptides, antibodies, folic acid and transferrin, allows selective transport and reduces unwanted effects for glioblastoma. CNTs can also be used for transport and delivery of various pharmaceuticals, and offer a multifunctional system toward the theranostic application for GBM.

Future research can synthesize biocompatible CNTs and develop personalized nanocarriers for treatment. The carriers can contain various combinations of stimuli-activated therapies. The efficacy of the carriers should be tested in preclinical and clinical studies. Advances in nanotechnology, molecular targeting, and precision medicine are expected to further enhance the therapeutic potential of CNT-based systems for glioblastoma.

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