

Nanofibers in Glioma Therapy: Advances, Applications, and Overcoming Challenges

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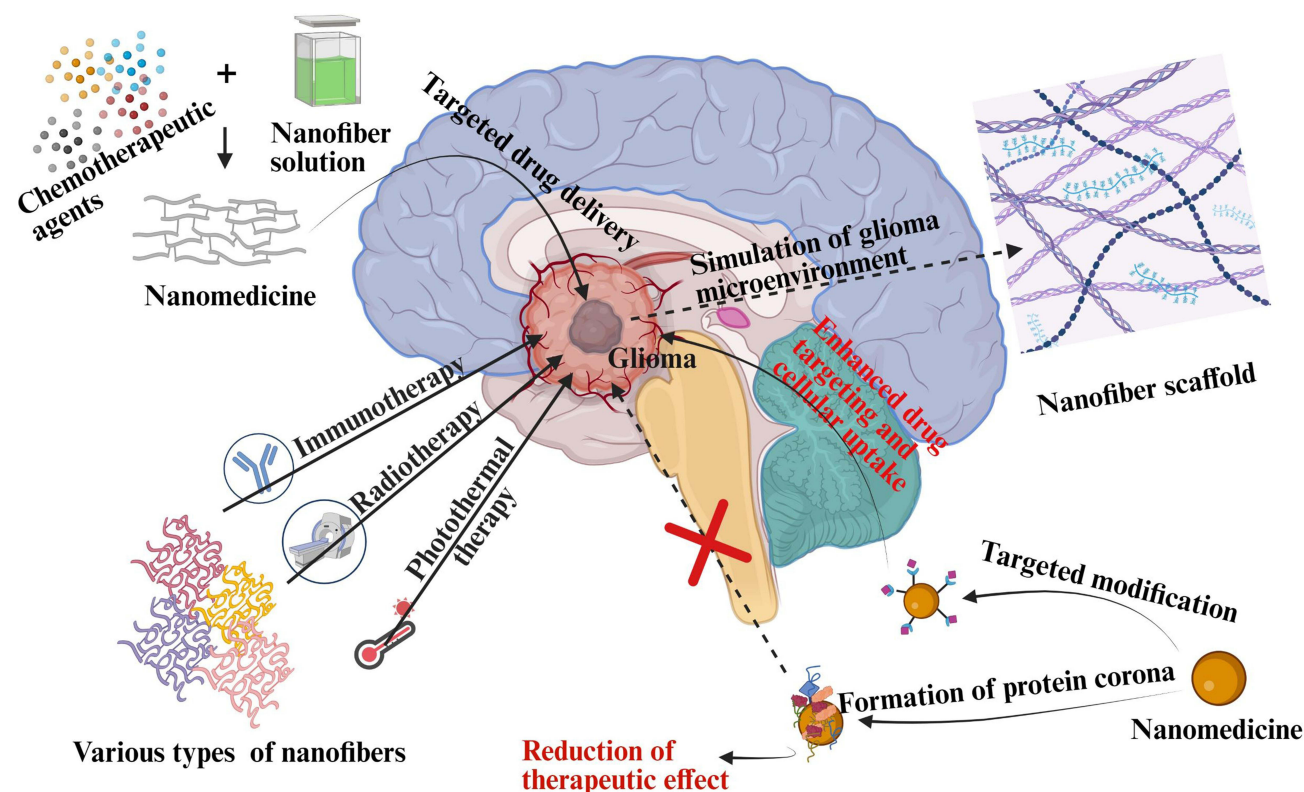
Abstract: Despite relentless effort to study glioma treatment, the prognosis for glioma patients remains poor. The main obstacles include the high rate of recurrence and the difficulty of passing the blood-brain barrier (BBB) for therapeutic drugs. Nanomaterials owing to their special physicochemical properties have been used in a wide range of fields thus far. The nanodrug delivery system (NDDS) with the ability of crossing the BBB, targeting glioma site, maintaining drug stability and controlling drug release, has significantly enhanced the anti-tumor therapeutic effect, improving the prognosis of glioma patients. Aligned nanofibers (NFs) are ideal materials to establish in vitro models of glioma microenvironment (GME), enabling the exploration of the mechanism of glioma cell migration and invasion to discover novel therapeutic targets. Moreover, NFs are now widely used in glioma applications such as radiotherapy, phototherapy, thermotherapy and immunotherapy. Despite the absolute dominance of NFs in anti-glioma applications, there are still some problems such as the further optimization of NDDS, and the impact of interactions between nanofibers and the protein corona (PC) on glioma therapy. This paper will shed light on the latest glioma applications of NFs in drug delivery systems and mimicking the tumor microenvironment (TME), and discuss how to further optimize the NDDS and eliminate or utilize the nanomedicine-PC interactions.

Keywords: nanofibers, glioma, tumor microenvironment, drug delivery systems, nanomedicine

Introduction

Gliomas are most frequent primary brain tumors of the spinal cord and brain.¹ Due to their special localization and invasive growth, malignant gliomas are characterized by high morbidity and mortality.² Especially, glioblastoma (GBM) is the most lethal type of brain tumors.³ The development of gliomas arises from a complex interplay between intrinsic genetic susceptibility factors and extrinsic environmental pathogenic elements. These genetic alterations propel cells into a state of perpetual cell cycle progression, enabling uncontrolled mitosis while simultaneously evading apoptotic mechanisms, growth inhibition, and immune surveillance. Furthermore, these mutations not only confer upon the cells the capacity to undergo metabolic reprogramming, facilitating abnormal energy metabolism that supports sustained proliferation, but also trigger tumor-induced angiogenesis and results in characteristic pathological changes, including hypoxia and necrotic regions within the tumor microenvironment.⁴ Despite active treatment, glioma patients show a poor prognosis with a median survival of 12 to 15 months.⁵ Due to intrinsic heterogeneity, as well as invasiveness and infiltration, natural protective barriers, and diversified mechanisms of chemotherapy and radiotherapy resistance, glioma treatment still faces tremendous challenges.⁶ The main reasons for poor prognosis of gliomas are the difficulty of complete resection during surgery, the high rate of recurrence after resection, and the high occurrence of chemotherapy resistance.⁷ Currently, surgery, radiotherapy and chemotherapy are still

Graphical Abstract



the mainstay for clinical management of gliomas. Surgery followed by radiotherapy and adjuvant chemotherapy is treated as standard therapeutic approach for glioma patients.^{8–11} On account of the limitation of surgery only applicable to low-grade gliomas,¹² the risk of death during surgery, affected by a complicated microenvironment,¹³ and the infiltration of tumor cells into normal brain tissues through blood vessels and white matter tracts,^{11,14,15} the surgery is not suitable for everyone. Furthermore, the recurrence can occur rapidly within a few centimeters (2cm) of resection site,¹³ through the resistance mechanisms of tumor inherent heterogeneity, intact blood-brain barrier (BBB), aggressive invasion and infiltration.⁶ Especially, the BBB, which is thought to be the intact physical barrier that maintains the integrity and homeostasis of the central nervous system (CNS), represents a huge obstacle for chemotherapeutics to penetrate, resulting in insufficient drug concentration to achieve the anti-tumor effect in the tumor site.¹⁶ The formation of blood-brain tumor barrier further compromises drug delivery efficacy, creating a pharmacologically privileged sanctuary for tumor cells. Of particular concern are glioma stem cells, which exhibit intrinsic treatment resistance and possess the capacity to orchestrate the tumor microenvironment through paracrine signaling, thereby maintaining their self-renewal and proliferative potential, making them the primary cellular reservoir for tumor recurrence and resistance development.¹⁷ For example, common chemotherapy agents for glioma treatment, such as Temozolomide (TMZ) are difficult to cross the BBB. In addition, they are characterized by instability, short half-life, high side effects and high drug resistance rate resulting in chemotherapy being ineffectual.¹⁸ Therefore, the local drug delivery systems (DDS) that can protect the chemotherapeutics before release and cross the BBB are urgently necessary.^{19,20} Moreover, gliomas exhibiting significant heterogeneity in their biological behavior, pathological characteristics, and clinical presentations can be classified into distinct histological subtypes, including astrocytomas, oligodendrogliomas, ependymomas, and pilocytic astrocytomas, each demonstrating unique morphological features, growth patterns, and prognostic outcomes. Furthermore, molecular heterogeneity is a hallmark of gliomas, particularly evident in GBM, where diverse transcriptional subtypes and subclonal populations exhibit variations in gene expression profiles,

therapeutic responsiveness, and clinical outcomes.⁵ Glioma inherent heterogeneity is another tricky issue hindering glioma treatment so that investigating glioma cell formation, progression and metastasis by simulated glioma microenvironment (GME) also presents the enormous potential for discovering new tumor treatment targets.^{14,21–23}

In recent years, nanofibers (NFs) have been in the spotlight owing to their various applications²⁴ in the treatment of multiple diseases, such as cancers,^{25,26} diabetes,²⁷ alveolar bone regeneration,²⁸ and peripheral nerve injury repair. Due to their significant advantages, such as high drug-loading capacity, low volume requirement, excellent biocompatibility, biodegradability, good conformity and easy codelivery of multi-chemotherapy agents,^{6,29} NFs have been designed to optimize the glioma therapy not only by improving encapsulation efficiency³⁰ and sustainably controlling drug release rates,^{31–33} but also by enabling biotherapeutic molecules (such as chemotherapy agents, nucleic acids, peptides, or imaging agents) to breach the BBB without interfering with the normal brain function.³⁴ Liposomes, NPs, and nanoenzymes exhibit superior performance in specific applications, but their overall performance and versatility are inferior compared with NFs. Specifically, liposomes and NPs are characterized by relatively simplistic structures and inferior mechanical properties, rendering them unable to offer brain extracellular matrix (ECM)-like support. And the sustained drug delivery capability is impeded due to the unclear toxicity of degradation products, and rapid degradation rates, thereby preventing the achievement of long-term controlled release. With the emergence of mature technologies such as electrospinning, NFs can be mass-produced at relatively low costs. Conversely, the production process of liposomes, NPs, and nanoenzymes is relatively complex challenging and costly.^{35–37} Nasir et al³⁸ pointed out that NFs could be utilized for the targeted delivery of agents into the glioma site. Therefore, NF-based target drug therapy has been regarded as an effective approach for localized cancer treatment, reducing systemic toxicities and side effects to normal cells.³⁹ Due to the mechanical and structural cues present in the ECM, aligned NFs with anisotropic, elongated structure and nanomorphology are capable of mimicking the GME accurately,^{40,41} which facilitates further exploration the mechanisms of tumor resistance and recurrence, and to achieving clinical practice, drug development, and biological research.

In this review, we will discuss the application of NFs in the treatment of gliomas, focusing on the delivery of anti-glioma drugs and the mimicry of microenvironment. Emerging issues will also be raised to further optimize the NFs-based delivery system and the clarification of interactions between NFs and the protein corona on glioma management was elucidated.

Synthesis Methods of Nanofibers

NFs are defined as nanomaterials with a size of 100 nanometers or less, with a length that can exceed the diameter by up to 100 times. Broadly, every fiber with a diameter less than one μm is considered an NFs.⁴² NFs can be divided into organic and inorganic NFs. Organic NFs are usually made from polymers, which are further divided into natural and synthetic categories, including polystyrene (PS) and poly(vinyl chloride) (PVC), poly(ϵ -caprolactone) (PCL), polylactic acid (PLA), and poly(lactic-co-glycolic acid) (PLGA), poly(vinylidene fluoride) (PVDF), polyaniline (PANi), and polypyrrole (PPy).⁴³ Inorganic NFs include carbon nanotubes,⁴⁴ silica NFs,⁴⁵ and nanosilicates-doped NFs, etc.⁴⁶ Owing to their unique combination of synthetic materials and fabrication techniques, NFs have a large surface area, high surface-to-volume ratio, favorable morphological properties, and excellent biocompatibility and biodegradability. In recent years, the promising applications of NFs in human cancers have displayed sustainable growth and are projected to have significant prospects in the future (Figure 1).

During last decades or so, variety of fabrication methods have been developed, even some of them have mainly been presented in investigation phase. Some natural, synthetic, and hybrid materials could be electrospun into NFs.^{47–49} These common synthetic approaches are composed of Electrospinning, Self-Assembly, and Three-Dimensional Printing (Table 1). Among them, Electrospinning technology is the most widely used and representative because of its prevalence in NFs manufacture.⁵⁰

Electrospinning

Electrospinning is a straightforward, cost-efficient, flexible, and widely used method that can deliver novel nanomaterials with controllable morphology and drug loading in one step by various materials.^{50,57} A basic electrospinning setup consists of three essential segments: a needle fitted with a metal nozzle, a collector for fiber deposition and a high voltage supply creating an electric field between the needle and the collector. Diverse liquids can be placed into the needle. Under low voltage, the spherical droplet is formed at the nozzle tip. As the voltage increases, the droplets spray out to form NFs

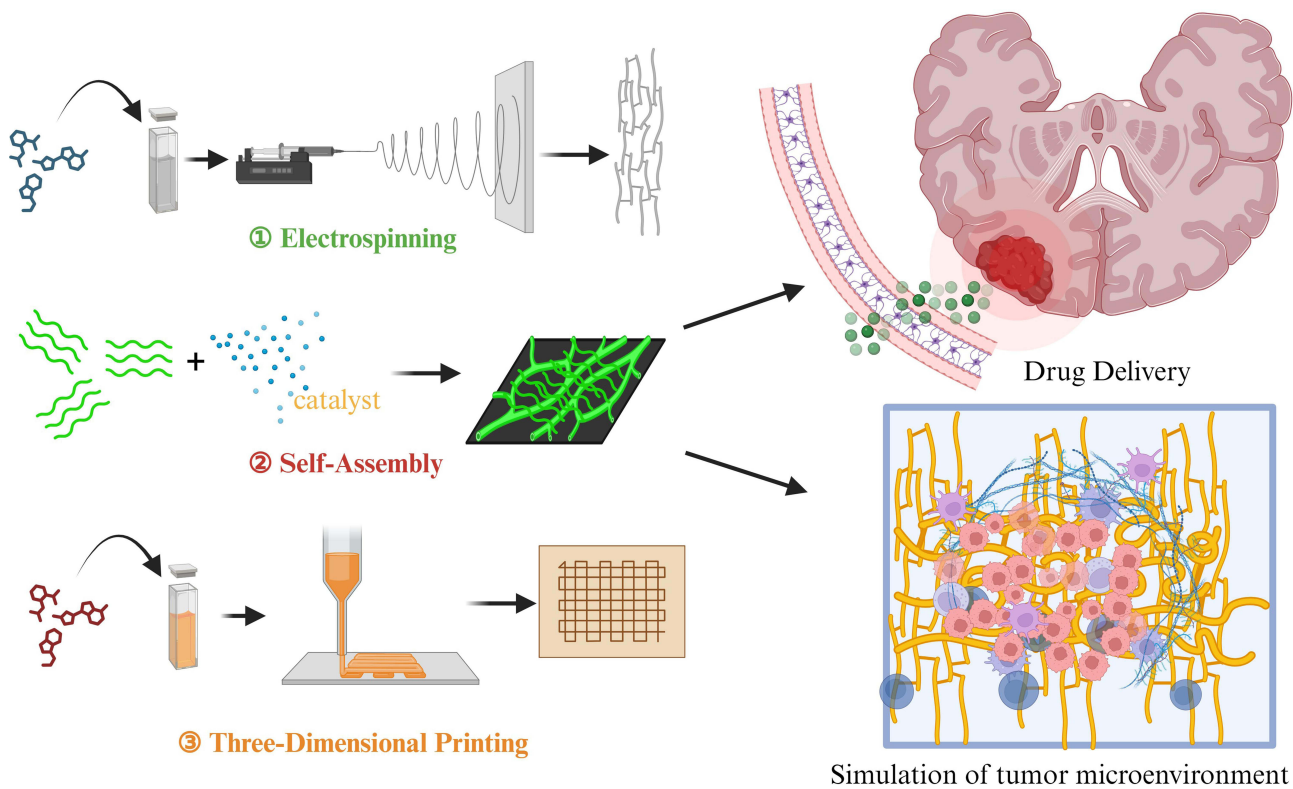


Figure 1 The synthesis and application of nanofibers in gliomas. Nanofibers are typically synthesized through electrospinning, self-assembly, and three-dimensional printing for drug delivery and microenvironment simulation of gliomas Created in BioRender. Zhou, (S) (2025) <https://BioRender.com/r41m582>.

towards the collector.⁵⁰ Electrospinning is for the large-scale production multiple materials into NFs with high surface area and porosity, allowing precise control over fiber diameter and shape via adjusting solution properties and process conditions. However, this method is constrained by several drawbacks, including the necessity for the spinnability of polymer solution, the toxicity of solvent residues, and the requirement of intricate collection devices when fabricating highly ordered fiber structures.⁵⁸ The electrospinning NFs have usually shown astounding features, including better uniformity, extremely large porosity and surface area, stronger mechanical strength, high loading capacity, excellent encapsulation efficiency, ease of modification, combination of diverse therapies, low cost, etc. These remarkable

Table 1 The Synthesis and Application of Nanofibers in Gliomas

Method	Flow Rate	Voltage	Materials	Application	Highlights	Refs
Electrospinning	5 mL/h	12kV	PLA	Encapsulation of OL, rutin and TMZ	Electrospun nanofibers demonstrated sustained drug release within 120 hours to combat recurrent gliomas effectively.	[51]
Electrospinning	NA	12kV or 18kV	PLA	Deliver PTX to glioma site	Electrospun nanofiber scaffolds can significantly improve the survival rate of mice by releasing PTX rapidly, moderately, and slowly.	[52]
Electrospinning	0.2mL/h	17 kV	PEDOT, CS, PEO	Promote glioma cell adhesion, proliferation, growth, and development under optimal external electrical stimulation	Nanofibers exhibit high electrochemical stability, high conductivity, and ultra-sensitive piezoelectric properties for various applications such as neural tissue engineering, and brain tumor research.	[53]

(Continued)

Table 1 (Continued).

Method	Flow Rate	Voltage	Materials	Application	Highlights	Refs
Electrospinning	1 mL/h	26 kV	PCL, Gel	Simulation of the extracellular matrix of GBM tumor	Nanofiber scaffolds showed the ability of enhancing axon growth and elongation, supporting communication between tumor cells and the microenvironment to trigger the process of tumor recurrence.	[54]
Self-Assembly	NA	NA	Hydrogel, Peptide	A biocompatible delivery depot of DOX and CUR, respectively	Electrospun nanofibers exhibited continuously release of DOX or CUR over 20 days, increased cell uptake and enhanced cytotoxic effects.	[55]
Three-Dimensional Printing	NA	NA	CNF, PCL	Provide support for the attachment, migration and targeted differentiation of nerve cells.	Nanofiber scaffolds support signal transmission and navigate neurons in a correct pathway towards the targeted end.	[56]

Abbreviations: OL, Oleuropein; TMZ, Temozolomide; PLA, polylactic acid; PTX, paclitaxel; PEDOT, shell/core poly(3,4-ethylenedioxythiophene); CS, chitosan; PEO, polyethylene oxide; PCL, polycaprolactone; Gel, gelatin; GBM, glioblastoma; DOX, doxorubicin; CUR, curcumin; CNF, carbon nanofibers; PCL, polycaprolactone.

properties reveal meaningful application potential in cancer diagnosis and therapy, especially in variety of DDS.⁵⁹ For example, the NF scaffolds have been used as implantable devices in cancer chemo-, photothermal, or hyperthermia therapy of solid tumors.⁶⁰ Nevertheless, electrospinning technology still remains several problems like sundry instabilities, such as spiraling, coiling, or bending, affecting fiber elongation and diameter fluctuations.⁶¹ Hence, to ensure that the manufactured NFs possess controlled and effective therapeutic effects, comprehensive consideration should be given to the properties of therapeutic ingredients, specific applications, delivery routes, and precautions for NFs manufacturing. Specifically, the therapeutic-related parameters can be divided into solution parameters (eg, molecular weight, solution concentration, solution viscosity, polarity, electrical conductivity, and solution surface tension), processing parameters (eg, feed and flow rate, voltage, orifice diameter, and nozzle-to-collector distance), and ambient parameters (eg, temperature and relative humidity).^{50,51,62,63} The molecular mass of raw materials plays a crucial role in determining the rheological properties and spinnability of the spinning solution. The viscosity and surface tension of the solution are critical factors that influence both the diameter and morphology of the fibers. Generally, higher viscosity or surface tension leads to the formation of fibers with larger diameters. Finer nanofibers can be achieved by increasing the electric field strength or by enlarging the distance between the needle tip and the collector. Additionally, the interaction between the electric field and the spinning solution is affected by the conductivity of the solution, further affecting the fiber diameter and morphology.⁵² Environmental factors also significantly influence the morphology of NFs. The temperature of the spinning environment influences the evaporation rate and solidification process of the spinning solution, while humidity affects the solvent evaporation rate. Consequently, the fiber diameter and surface morphology can be modulated by adjusting the temperature and humidity conditions. Furthermore, the fiber morphology can also be influenced via the atmospheric conditions in the spinning environment, such as vacuum, air, or other gases. These factors collectively determine the final characteristics of the NFs produced.⁵³ Coaxial electrospinning, emulsion electrospinning and side-by-side nozzle electrospinning are improved based on electrospinning. The inner and outer channels of coaxial electrospinning can load different polymer solutions, forming NFs with core/shell structures, making their morphology more diverse.⁶⁴ Emulsion electrospinning is to disperse one substance in the form of emulsion in another substance, and then spins this emulsion into NFs through electrospinning process, which is more convenient and shows greater expansion potential compared with coaxial electrospinning.⁶⁵ Side-by-side nozzle electrospinning is a nozzle with parallel channels that can simultaneously spin multiple polymer solutions.⁶⁵ However, with the electrospinning technology becoming more mature, electrospun NFs have been widely used in glioma applications as chemotherapeutic drug carriers. For example, electrospun NF can achieve the control release of TMZ, resulting in rapid inhibition of cancer cell viability and effective inhibition of postoperative GBM recurrence⁵⁴ (Figure 2). Electrospun nanofiber scaffolds

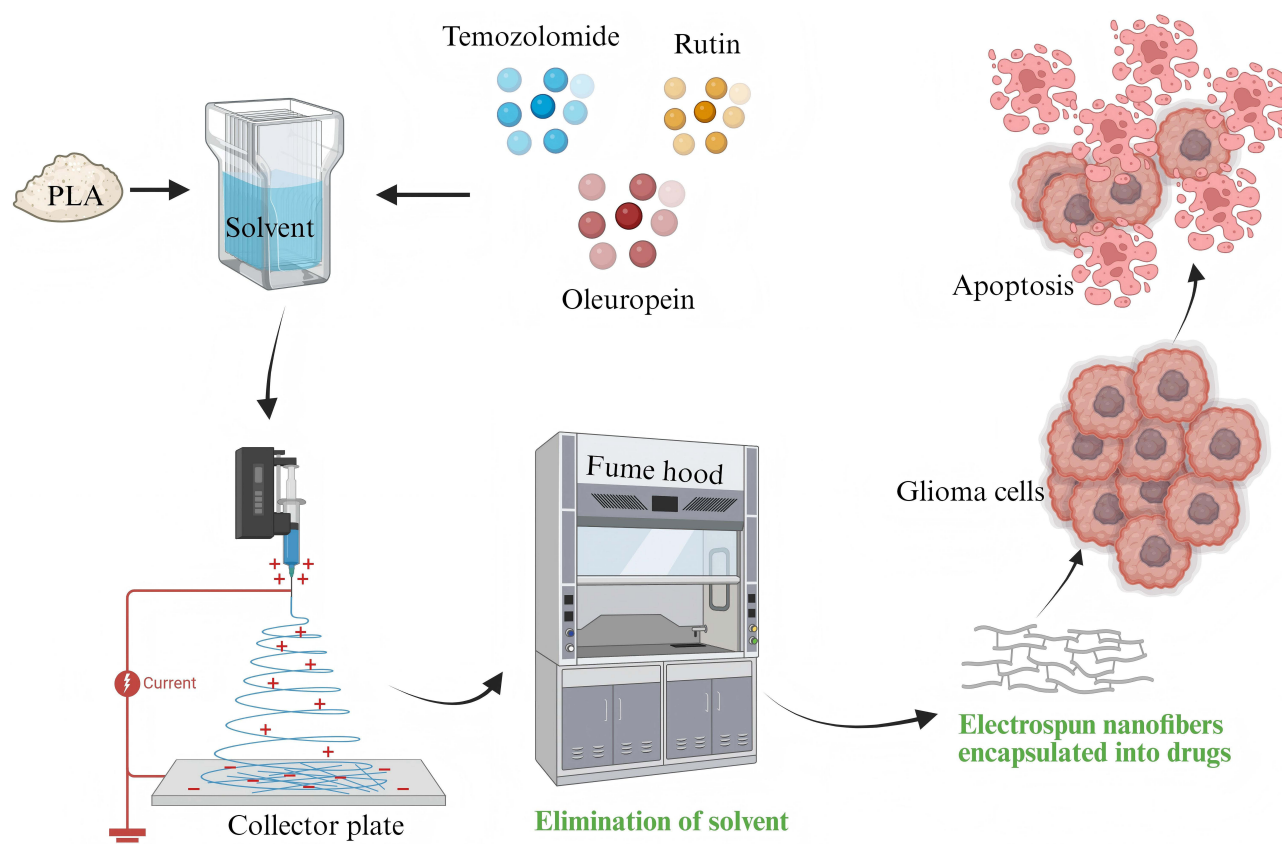


Figure 2 Effective application of nanofiber drug delivery system in glioma treatment. Through electrospinning technology, Temozolomide, Oleuropein or rutin were encapsulated within nanofibers, followed by solvent evaporation in a fume hood. These drug-loaded nanofibers were subsequently applied to treat glioma cells, inducing significant apoptosis in the targeted cell population. Created in BioRender. Zhou, (S) (2025) <https://BioRender.com/sl9j395>.

demonstrated a unique range of drug release rates. When reaching the tumor site, the scaffold can release the drug rapidly to achieve superior anti-tumor effects, greatly improving the treatment of malignant gliomas.⁶⁶ What's more, nanofiber scaffolds can provide 3D structures and programmed electrical signals consistent with cell survival thus can be used to mimic the GME.⁶⁷ Composite nanofibrous scaffolds, successfully prepared by electrospinning, are beneficial for improving axon growth and elongation as well as supporting the interplay between cancer cells and the GME, thus leading to tumor recurrence, making it an excellent candidate for simulating the GME.⁶⁸

Self-Assembly

Self-assembly is a natural process propelled by various non-covalent interactions, including aromatic stacking, electrostatic and/or hydrophobic, metal coordination interactions or hydrogen bonding,⁵³ possessing the capability to produce ultrafine NFs with diameters less than 10 nm and generate NFs endowed with specific functionalities, such as targeted drug delivery, but with the disadvantages of the complex production process and the limitation of large-scale production.⁶⁹ The main types of self-assembly structures are composed of peptides, polymers, and metal-based structures.⁷⁰ Based on self-assembly technology, the NFs have the characteristic of mimicking biological processes and functions of fibrous structures.⁷¹ Furthermore, the self-assembled high-aspect ratio NF structures have the commendable functions of prolonging blood circulation time, widening the biological distribution, improving targeting efficiency, changing cell uptake and even different intracellular deposition.⁷² Recently, the self-assembled NFs have been widely applied to biomedical applications involving drug delivery, tissue engineering, bacterial infection, and cancer treatment.^{55,73} In particular, due to their in-situ assembly with spatiotemporal responsiveness and diverse biological activities, self-assembled NFs exhibit enormous potential for cancer treatment through mechanisms of blocking blood vessels, seizing cells, hampering cell communication, delivering anticancer agents, inducing cell apoptosis, and enhancing immunity.⁷⁴ In one study, peptide NFs were formed by self-assembly at the glioma site, which can deliver both water soluble and

insoluble drugs. For instance, when delivering Doxorubicin (DOX), higher cellular uptake and enhanced cytotoxic effects were observed; when delivering curcumin, the result showed higher levels of early apoptosis, demonstrating the potential of self-assembled NFs in chemotherapeutic drug delivery.⁵⁶

Three-Dimensional Printing

Additive manufacturing or three-dimensional (3D) printing is used to produce layer-upon-layer structures with the help of computer-aided design (CAD). It can be performed in multifarious techniques such as 3D electroprinting, inkjet printing or extrusion printing consistent with the prepared material to create drug delivery platforms, prosthetics and tissue scaffolds,⁷⁵ exhibiting the advantages of high precision, the ability of complex structural design, and personalized customization options. However, it suffers from low generation efficiency and high costs, thereby rendering it unsuitable for large-scale production.⁷⁶ The matrices for cells or bioactive molecules made of polymers such as polysaccharides, gelatin and silk have a tremendous potential in regenerative medicine.⁷⁷ For example, one study showed printed NFs can provide support for neuronal cell growth, differentiation and migration, providing a beneficial tool for in vitro glioma research.⁷⁸

Multiple Applications of Nanofibers in Glioma Treatment and Research

In promising studies, unique advantages of NFs have raised a research boom for their potential applications in biomedicine applications including DDS, tissue engineering, wound healing, disease diagnostics, biosensors, biocatalysts, supercapacitors,^{79–85} regenerative medicine,⁸⁶ and other applications involving food and plant science,⁸⁷ cosmetics,⁸⁸ etc. To date, with the increasing research on the applications of anti-tumor treatment of NFs, it has been discovered that NFs have significant advantages in local DDS, simulating TME, and other aspects. For the anti-glioma application, NFs-based systems exhibit several notable abilities, such as crossing BBB characteristics, targeting tissue specificity, controlling drug release, and reducing systemic toxicity. Furthermore, aligned NFs are capable of mimicking the microenvironment, demonstrating enormous potential in glioma research and treatment.

In the field of oncology, NFs are mainly utilized for the diagnosis (eg, diagnostic tools⁸⁹ and biomarker detection⁹⁰), the treatment (eg, photodynamic therapy (PDT), magnetic hyperthermia therapy, targeted drug delivery^{91,92}), and clinical investigation like biomimetic TME models for drug screening and tumor progression screening.⁹³ Based on the unique properties of gliomas, nanotechnology as an innovative anti-cancer technology has been rapidly developing to overcome a series of issues with conventional chemotherapeutics including non-specific biodistribution and targeting, poor water solubility, short half-life, difficulty in crossing the BBB, low oral bioavailability and therapeutic indices.^{94–96} Zhu et al demonstrated that the recurrence of postsurgical glioma is apparently inhibited by the multi-responsive NFs loaded with TMZ, reflecting superior capability of nano-carriers against glioma.⁹⁷ The NFs scaffolds with 3D fibrous structures display the ability to reproduce heterogeneity, directionality, and surface chemistry related to glioma cell behaviors,⁹⁸ and could serve as outstanding platforms for stimulating the extracellular microenvironment in vitro. For example, Marhuenda et al⁹⁹ designed a 3D-ex-polyacrylonitrile NFs with adjustable stiffness to mimic the brain ECM, which facilitated glioma cell migration by catalyzing the formation of multi-branched N-glycans. In short, NFs-based nanomaterials have shown great potential in the diagnosis and treatment of glioma and are worth further investigation.

Nanofiber as an Effective Tool for Simulating the Glioma Microenvironment

At present, numerous studies have shown that GME plays an indispensable role in tumor formation, progression, and metastasis, cancer cell behavior, angiogenesis, immune escape, and drug resistance.^{41,100,101} For instance, the main pathway of glioma cell infiltration is through ECM-mediated cell locomotion on the surface of blood vessels and white matter tracts.^{102,103} Glioma stem cells are crucial for remodeling the GME to maintain a favorable environment for tumors.¹⁰⁴ Additionally, the codependent cholesterol metabolism within the TME promotes the malignant progression of GBM by inducing phagocytic dysfunction of macrophages,¹⁰⁵ further exacerbated by M2 macrophages and the deficiency of cytotoxic T cells.^{106,107} Based on the above facts, the recent trend is to discover new therapeutic targets by studying the GME to improve glioma treatment. And then, it is both urgent and necessary to create a 3D biological scaffold to establish the in vitro GME models to study the mechanisms of tumor occurrence, development, and migration in order to seek novel therapeutic targets.

The most representative model for GBM cell invasion in vitro is the slice assay in which glioma cells are seeded on brain slices reproducing their behaviors. Nevertheless, this method is limited because the brain slices are difficult to maintain in vitro.^{9,108} The most common models used to study the migration and invasion of glioma cells are the hydrogels made of collagen, fibronectin, or laminin. However, these isotropic hydrogels do not replicate the directional mechanical force present in the brain ECM.⁴⁰ Besides, 2D models of cell migration, such as the monolayer wound-healing assay, microliter scale migration assay, and Boyden chamber assays, have been employed to investigate GBM cell migration but the main drawbacks are the differences in the mechanical environment and low physiological correlation with brain tissue.¹⁰⁹ All the mentioned methods are limited by various drawbacks.¹¹⁰ Luckily, the rise of NF scaffolds has provided tremendous assistance for establishing in vitro glioma models.¹¹¹

Based on their unique features of large surface area, special morphological structure, high biocompatibility, physico-chemical properties similar to brain tissue as well as mechanical and biochemical signals that promote nerve regeneration, NFs have become excellent materials for creating GME models to discover new therapeutic targets by investigating the mechanisms of glioma cell migration and invasion^{112–114} (Figure 2). Nanomorphology may have an advantage in replicating similar mechanical properties in in vitro GME models compared to in vivo glioma ECM.^{115–117} Moreover, on aligned NFs, the velocity of cell migration is 4.2 ± 0.39 micrometers/hour, which closely resembles the spreading of glioma cells in white and gray matter observed in the brain. And the morphology of the aligned NFs promotes cell penetration, enabling time-lapse analysis of cell migration and potentially supporting identification of physiological medium and pharmacological inhibitors of invasion.¹¹⁸ It is well documented that multiple NF-based scaffolds have been used in GME studies.

In the first attempts, to investigate the effect of NFs morphology on cell migration ability, chitosan-polycaprolactone (C-PCL) composite NFs were designed and fabricated with diameters of 200 nm, 400 nm, and 1.1 μ m, which could be oriented randomly or aligned into different nanotopographies. Human U-87 MG GBM cells were cultured on different nanofibrous substrates. The results proclaimed that aligned NFs with small diameter (200 nm and 400 nm) induced maximum phenotypic change indicative of invasive behavior on human GBM cells. In addition, cells cultured on 400 nm aligned NFs exhibited migration characteristics similar to those reported in vivo.⁴⁰ At the same time, aligned NFs biomaterials produced by core-shell electrospinning that can emulate the morphological properties of white matter bundles, allowing systematic investigation of the effects of mechanical and chemical properties on GBM cell adhesion and migration. The data revealed that cell morphology, migration rate, and sensitivity of GBM to NFs mechanics were strongly dependent on NFs modulus, providing a favorable platform for further research on the complicated interaction of chemistry, mechanics, and morphology in influencing brain tumor behaviors.¹¹⁹ Furthermore, aligned NFs membranes were used to explore the mechanical features of GBM cells in vitro. The data showed that GBM cells had significantly lower cytoskeletal stiffness, cellular traction stress, and adhesion patch area in comparison with healthy astrocytes. GBM cells cultured on aligned NFs hold elevated migration capability and remarkably reduced cytoskeletal stiffness. Similarly, this experiment indicate the research potential of aligned NFs in GME models in glioma studies.¹⁵

In the latest study, more diverse nanofiber scaffolds have been used in studies related to glioma research. On the basis of the previous work, their functions as GME models have been further improved. In the presence of ECM, the PCL-based NFs can meet the growth and migration of human glioma cells and rat astrocytes. This result revealed that astrocytes interact with GBM cells via a multitude of pathways, including direct contact and soluble factors, demonstrating demonstrated the meaningful potential of NFs to duplicate some physical and physiological characteristics of GME, allowing analysis of topographical effects in metastasis of glioma cells to search for novel targets for treating gliomas.¹²⁰ The C-PCL polyblend NFs with added HA, exhibited a distinctive morphology and surface chemistry that increases cell displacement and cell velocity and demonstrated greater cell migration speed and more resistance to cell death when exposed to the TMZ, indicating that it serves as a superior in vitro platform for studying highly invasive GBM cells and anti-invasive therapeutics.¹⁰³ Electroactive NFs scaffolds were known as their excellent programmed electrical signals to cells, but their inherent non-biodegradability was a huge obstacle hindering their widespread clinical application. To overcome the issues mentioned above, NFs combined with poly(3,4-ethylenedioxythiophene) and chitosan (PEDOT/CS) were synthesized. The results indicated that PEDOT/CS NFs were provided with inimitable electrical properties including high electrochemical stability, ultra-sensitive piezoelectric characteristics and high electrical conductivity, enabling their use to mimic the growth, development, proliferation and invasion of glioma cells under a perfect external electrical stimulation and 400mV/pulse voltage.⁶⁷ Moreover, the printed

PCL films exhibited 30% higher mechanical properties than pure PCL films, which was highly comparable to human nerves, supporting cell adhesion, migration and differentiation to the desired endpoint in an in vitro cellular study of human glioma cells.⁷⁸ Spiropyran-based NFs with high spatiotemporal precision supporting reversible and remote cell manipulation exhibited outstanding biocompatibility and negligible toxicity to C6 glioma cancer cells for 5 days. Photoreversible cell adhesion results presented visibly switchable attachment and detachment of C6 cells via alternate UV and visible light irradiation, showing great potentiality of nanotechnology to probe glioma cell attachment and detachment in a reversible way.¹²¹ In short, aligned NFs have great potential in providing an exceptional in vitro model for the development of anti-invasive therapies to treat gliomas.

Though NFs have an advantageous ability in mimicking the microenvironment, their diameters, densities, alignments, and surface nanotopography have all been shown to significantly affect on the neuronal and cellular behavior.^{112,122} To conserve mechanical properties in the models, substances such as HA, collagen, polymer, and Matrigel have been added. Among them, highly arranged NFs containing HA exhibit stronger hydrophilicity than random fibers, enabling improvement of cell adhesion and proliferation. However, another study presented negative effects of HA on cell migration.^{119,123,124} Therefore, further studies are needed to investigate the surface physicochemical properties of NFs scaffolds integrated with various biomaterials.

Nanofibers Serve as an Effective Strategy for the Delivery of Anti-Glioma Drugs

Chemotherapy, a less invasive therapy, is generally considered a more common treatment approach. In recent years, diverse anticancer drugs such as Paclitaxel (PTX), TMZ, Carmustine (BCNU) and DOX have been applied to the treatment of glioma. However, these anticancer drugs have drawbacks such as instability, a short half-life, difficulty penetrating the BBB and insufficient concentration in tumor vicinity, resulting in systemic side effects and poor prognosis in glioma patients.⁹ Fortunately, the emergence of NFs has changed this situation.¹²⁵ Nanofibers serve as an effective

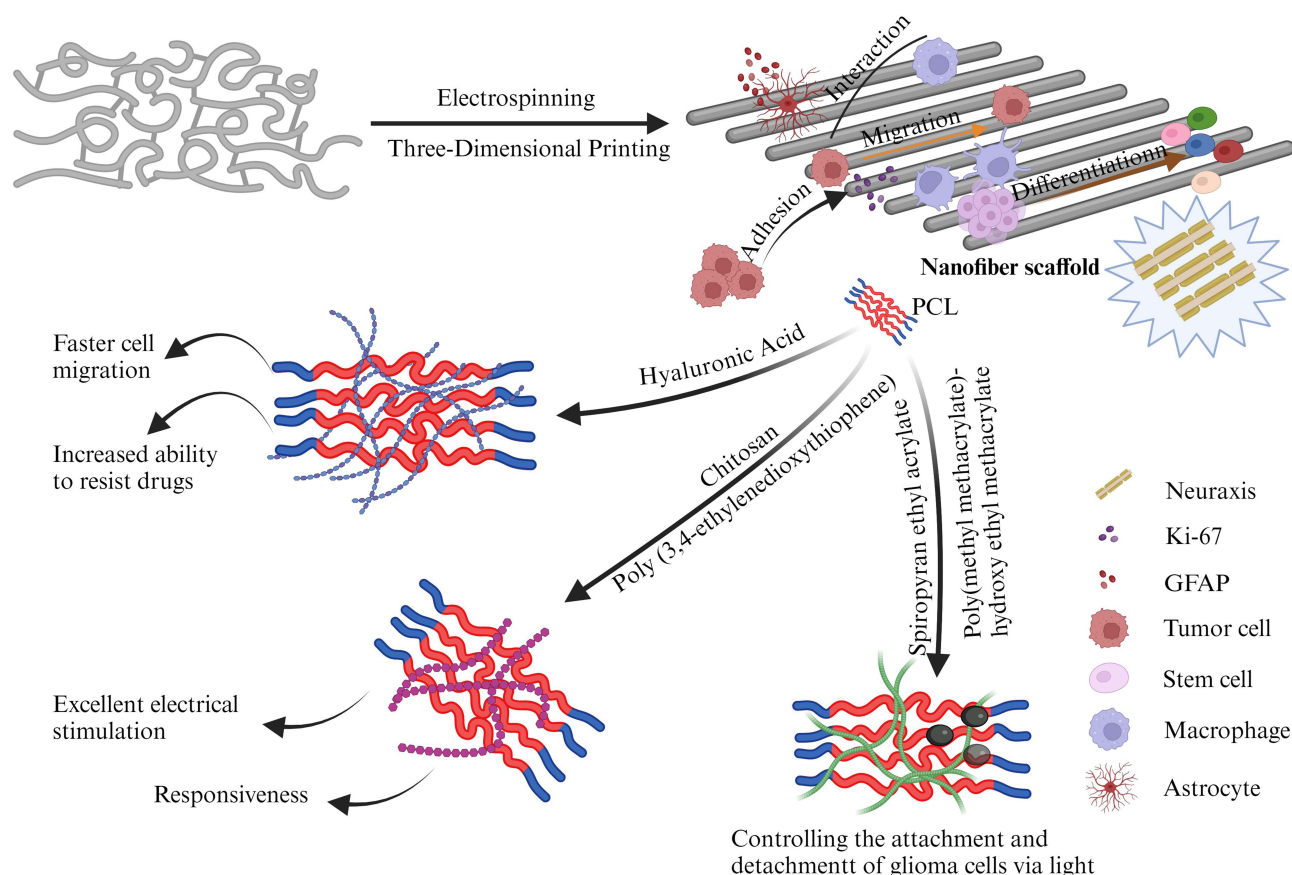


Figure 3 Nanofiber in simulation of glioma microenvironment. The nanofiber scaffold supports the growth and migration of glioma cells as well as cell interactions. By adding different components to the scaffold, the functionality of the nanofiber scaffold can be further optimized. Created in BioRender. Zhou, (S) (2025) <https://BioRender.com/m14k458>.

strategy for delivering anti-glioma drugs, which greatly enhance the ability of drugs to cross the BBB, and then show higher anti-glioma efficacy (Figure 3). These NDDS present outstanding abilities in drug delivery due to their large surface area, high encapsulation, and excellent multidrug loading capacity, drug controlled release¹²⁶(Table 2), and improvement of the physicochemical and pharmacokinetic properties of drugs¹²⁷ (Table 3).

TMZ, the DNA-alkylating agent, is the first-line anti-cancer drug for glioma, typically used as adjuvant chemotherapy following surgical resection and radiotherapy.¹³⁴ It works via the mechanism of inducing the formation of the methyl adducts N7-methylguanine, O6-methylguanine, and N3-methyladenine in the DNA, finally leading to cell apoptosis.¹³⁵ To some extent, TMZ which is capable of traversing the BBB¹³⁶ can extend postoperative survival, however, the biggest challenge is that at least 50% of patients eventually have no response to TMZ.^{137,138} Next, there are drawbacks such as poor water

Table 2 Advantages and Disadvantages of Different Types of Nanofiber Drug Delivery Systems

Nanofibers/ DDS	Advantages	Disadvantages
Natural polymer nanofibers	High biocompatibility and low toxicity degradation products	Poor mechanical force and rapid degradation without long-term therapeutic effect
Synthetic polymer nanofibers	Excellent mechanical force, adjustable degradation rate and suitable for large-scale production	Low biocompatibility and toxicity of degradation products
Inorganic nanofibers	High mechanical force and thermal stability	Low biocompatibility and Difficult to degrade
Peptide-based nanofibers	Ultra fine fiber diameter (<10 nm), high biocompatibility and bioactivity and targeting	High cost and difficult to mass produce
Composite nanofibers	Functional diversification (such as adding drugs, growth factors)	Complex preparation process

Abbreviation: DDS, Drug delivery system.

Table 3 Drug-Loaded Nanofibers for Local Chemotherapy of Gliomas

Nanofibers	Drug	Cancer Cell	Cancer in vivo	Highlights	Refs
T/PPS	TMZ	C6, U87	NA	The nanodrug targeted to the postsurgical environment and achieved responsive and sustained drug release to inhibit local recurrent glioma after surgery	[94]
PLGA-PLA-PCL	TMZ	U87MG, C6	NA	Nanofiber carrier exhibited highly controlled drug delivery for a long time to hinder glioma recurrence	[128]
PLGA-PEG	PTX	U87MG-Red-Fluc cells	U87MG-Red-Fluc xenografts in mice	PLGA-PEG crossed the BBB and to improve the efficacy of loaded cargo	[129]
ac-(RADA)4-CONH2	DOX, CUR	U-87 MG	NA	The complex increased cellular uptake, higher cytotoxic effects and higher levels of apoptosis	[73]
Chitosan-coated PLGA NPs	BCNU	U87 MG	C6-bearing mice/rats	The complex has targeted drug transport capacity and efficient induction of cancer cell apoptosis through intranasal administration	[130]
Nanofibrous membranes	BCNU, irinotecan, CB	NA	Wistar rats	Nanofibrous membranes showed sustained release of high levels of drugs for more than eight weeks	[14]
Polypeptide nanofiber hydrogel	Metformin	GL261, U251, and U87	C57BL/6 mice	Sustained drug release and enhanced killing effects on GBM in vitro and in vivo	[131]
PEO, PLA	Rapamycin	U251 and U87	NA	Rapamycin released from NFs decreased cell viability of both U251 and U87 human GBM cells efficiently	[132]
PVA	DTIC	U87MG	NA	PVA presented high drug loading of $83.9 \pm 6.5\%$, good stability and mechanical properties and sustained drug release	[133]

Abbreviations: ac-(RADA)4-CONH2, an in-situ self-assembling peptide nanofiber hydrogel; BCNU, carmustine; CB, cisplatin; CUR, curcumin; DTIC, dacarbazine; NPs, nanoparticles; PCL, poly(ϵ -caprolactone); PEG, polyethylene glycol; PEO, polyethylene oxide; PLA, polylactic acid; PLGA, poly(lactic-co-glycolic acid); PTX, paclitaxel; PVA, polyvinyl alcohol; T/PPS, reactive oxygen species-triggered poly(propylene sulfide) 60 mixed with matrix metalloproteinases-responsive triglycerol monostearate lipids; TMZ, temozolomide; NA, not applicable.

solubility, rapid elimination, and unexpected side effects.^{128,139} TMZ encapsulated into NFs can effectively overcome the drawbacks of TMZ, efficiently preventing tumor resistance. The multi-responsive NFs composite hydrogel was used to suppress postoperative glioma recurrence. The results confirmed the responsive release and sustained release of TMZ encapsulated in this hydrogel in the resection cavity, revealing excellent anti-glioma performance in incomplete glioma resection models while minimizing systemic toxicity.⁹⁷ The hybrid-structured nanofibrous membrane (HSNM) as a novel drug carrier can transport a high concentration of TMZ to glioma site. In experiments of rats followed by surgical craniectomy, HSNM demonstrated the ability to sustain the release of TMZ for over 14 weeks and supported chemoprotective gene therapy which can improve chemotherapy tolerance and efficacy, significantly retarding and restricting tumor growth, reducing recurrence rate and prolonging survival time.¹⁴⁰ PLGA-PLA-PCL polymeric nanofiber implants can sustain the release of TMZ for days or months at the glioma site by switching different fibers with the negligible leakage of TMZ into the peripheral blood, which effectively reduces the recurrence of gliomas and prolongs the median survival period of the animals, suggesting the potential benefits of NFs in controlling GBM recurrence and improving prognosis.¹⁴¹

PTX is one of the most successful and effective drugs ever used in cancer chemotherapy, which have been used to treat a variety of cancer types,^{142,143} such as mastocarcinoma, lung carcinoma, brain cancer, and ovarian carcinoma.¹⁴⁴ The mechanism is to stabilize microtubules, thereby blocking cell mitosis and preventing effective division of cancer cells, ultimately leading to death. However, overexpression of P-glycoprotein (P-gp) and alterations in microtubules results in drug resistance in cancer cells, hindering the use of PTX in chemotherapy.^{145,146} Besides, its poor water solubility, low bioavailability, short half-life, and systemic toxicity can negatively impact clinical efficacy.^{129,147} To overcome these unexpected problems, diverse NDDS have been designed and fabricated. The acetalated dextran (Ace-DEX) nanofibrous scaffolds presenting an attractive PTX controlled release capability leading to a 78% long-term survival rate in GBM mice treated with surgical resection. And the nanofibrous scaffolds were acid-sensitive and responsive to the acidic environment of GME, resulting in higher PTX concentration at the tumor site compared to non-acid-sensitive PLA scaffolds.⁶⁶ Moreover, another NFs-based drug carriers with magnetic properties can achieve target transport and controlled release of PTX under alternating magnetic field, demonstrating extraordinary anti-U-87 MG efficacy in chemotherapy/thermal combination therapy.¹⁴⁸ A mixed NFs-based NP demonstrated significant improvement in PTX brain accumulation and meaningful advancement in survival rate of mice with similar biosafety compared to soluble PTX, showing the merits and potential of NFs in DDS.¹⁴⁹

DOX, the anthracycline antibiotic, is one of the most effective and versatile chemotherapeutics, yet its application is greatly restricted by limited BBB permeability¹⁵⁰ and side effects such as myelosuppression, vomiting, diarrhea, and particularly severe cardiotoxicity.^{151,152} It functions by various mechanisms such as DNA intercalation, free radical generation, and topoisomerase II dislocation, all of which lead to cellular damage.¹³⁰ DOX with the help of NFs is capable of easily passing through the BBB and accurately targets the tumor site. Additionally, DOX and nanocarriers usually have synergistic anti-tumor effects, further reducing the systemic side effects of DOX.⁶⁰ A self-assembling peptide nanofiber hydrogel was designed and prepared to deliver DOX, not only fully releasing DOX in four days but also showing increased cellular uptake and greater cytotoxic effects of DOX.⁵⁶ DOX encapsulated in NF-based liposomal nanoparticles (NPs) enabled drug-controlled release, enhanced therapeutic efficacy and reduced side effects of DOX more efficiently. The data revealed that NFs-based NPs significantly increased the cytotoxicity of DOX in rat glioma C6 cells, and minimally reduced body weights of mice compared to free drug.¹⁵³

BCNU belongs to the class of nitrosoureas which exerts anti-cancer effects via DNA alkylation, has severe toxicity to the bone marrow, kidneys and liver. Carmustine wafers (CW), the first approved wafer for treating high-grade gliomas, was implanted into the resection cavity, thereby improving patient survival and reduced systemic side effects. However, this approach is limited by invasive administration and adverse events such as infection, hydrocephalus, and wound healing complications.^{131,132} Fortunately, NFs-based drug carriers allow targeted transport of BCNU to the tumor site and local release of BCNU to reach enough drug concentration, thereby minimizing systemic toxic effects. For instance, BCNU placed in NFs composites showed significant anti-tumor properties against U251 human glioma by significantly reducing cell viability and increasing apoptosis rate (62.31%).¹³³ Another nanofibrous membrane can also sustainably release high concentrations of BCNU at the tumor site for more than 14 weeks, demonstrating therapeutic advantages in delaying and limiting tumor growth, prolonging survival time, and attenuating malignancy.¹⁴⁰

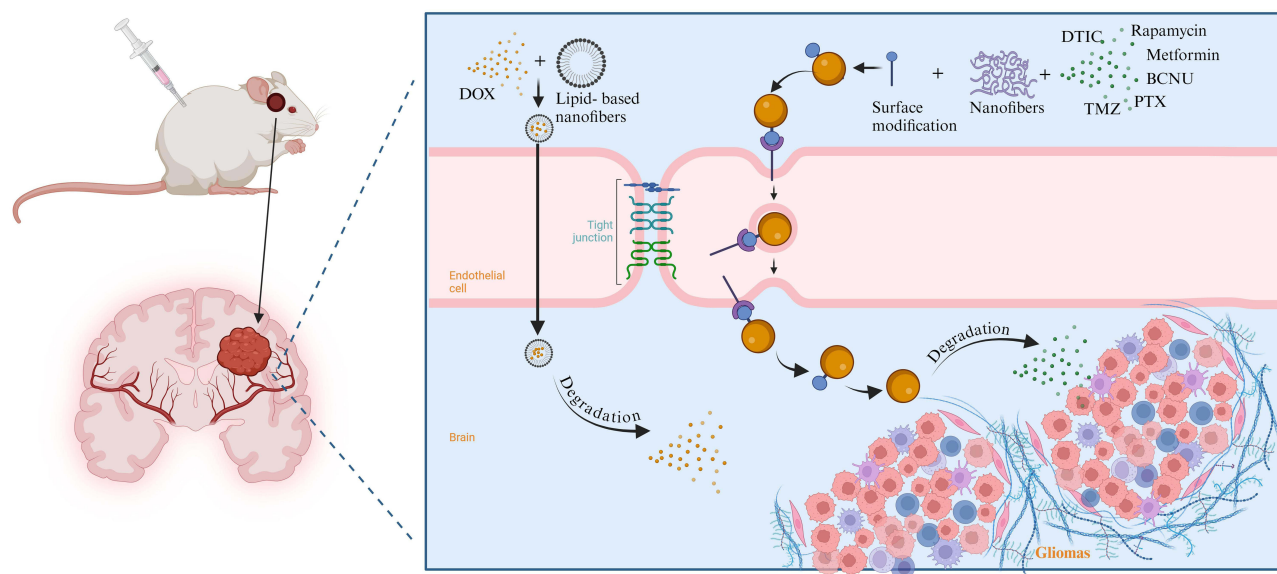


Figure 4 The way of nanomedicine crossing the blood-brain barrier. After entering the systemic circulation, nanomedicine can cross the blood-brain barrier via surface modification and target the tumor site, and then showing sustained drug release through slow degradation achieving anti glioma effect for a long time Created in BioRender. Zhou, (S) (2025) <https://BioRender.com/e66j862>.

In addition, NFs have exhibited excellent anti-glioma advantages when loaded with other drugs. Peptide hybrid NFs loading immunomodulatory agent metformin can activate the innate and adaptive immune system via inducing continuous CD8 T cell responses, facilitating M1 macrophage polarization, and regulating the expression of PDL1, HIF1- α , and CXCL9 in GME, showing an excellent therapeutic effect and eminent biosafety and exhibiting prolonged release curves along with enhanced GBM killing effects both in vitro and in vivo, providing a promising strategy for developing novel treatments for gliomas¹⁵⁴(Figure 4). PLA and polyethylene oxide (PEO), as biodegradable NFs, can overcome the disadvantage of rapamycin not being able to target tumor sites with marvelous and stable encapsulation efficiency. A correlation has been observed between sustained drug release and glioma cell toxicity, while limiting side effects, demonstrating great potential for inhibiting local recurrence following glioma surgical resection.¹⁵⁵ Polymer NFs loaded with Dacarbazine (DTIC) exhibited high drug loading capacity, excellent stability and mechanical properties, and sustainable drug release, improving the pH of GME, leading to cell death through DNA damage and apoptosis. The results revealed that NFs are great potential materials in improving DDS for gliomas.¹⁵⁶

More Advantages on Nanofiber-Based Local Therapy Than Systemic Therapy

Systemic therapy, a conventional treatment, can address the potential presence of microscopic metastatic or recurrent glioma cells and combating the systemic pathological changes caused by glioma.¹⁵⁷ In one clinical trial, a cellular therapy with a combination of steroids demonstrated tumor shrinkage and necrosis in more than half the number of patients treated, and an antibody response against the cells was detected in only one patient, reflecting the anti-tumor activity and fewer side effects of systemic therapy.¹⁵⁸ However, many problems also exist. For example, chemotherapeutic drugs are difficult to maintain stability in body fluids and difficult to cross the BBB. Moreover, high drug toxicity and drug resistance remain obstacles to chemotherapy. These deficiencies result in low drug concentration in the tumor site, thereby reducing the therapeutic efficacy and increasing toxic and side effects.^{31,159} Fortunately, the emergence of nanomaterials has revolutionized the treatment dilemma of gliomas. Currently, NDDS are being widely studied due to their unique advantages. A transformable self-assembling peptide with the properties of glutathione peroxidase 4 (GPX4)-protein-targeting and alkaline phosphatase (ALP)-responsive self-assembled into NPs under water-based conditions and then transformed into NFs in response to ALP during lysosomal/endosomal uptake in tumor cells to enhance lysosomal membrane permeability (LMP). The NFs not only targeted GPX4 and selectively degraded GPX4 protein under light, inducing ferroptosis, but resulted in further amplified ferroptosis via a Fenton reaction cascade due to a large

amount of leaked Fe²⁺, enhancing tumor immunotherapy efficacy.¹⁶⁰ NFs produced by PVA encapsulated with TMZ, maintaining drug stability, not only enhances drug uptake by U87MG cells, but also sustains the release of TMZ at the tumor site, improving antitumor effects and reducing systemic side effects, suggesting that NDDS may be a useful therapeutic strategy for treating GBM.¹⁶¹ Compared to the systemic therapy, local therapy may offer greater advantages in enhancing treatment efficacy and reducing toxic and side effects. NFs have significantly aided in targeted drug delivery,¹⁶² but few nanofiber formulations are currently used for clinical applications. Future efforts are in demand to make NFs available for clinical indications as soon as possible.

Nanofibers in Radiotherapy for Gliomas

Currently, NFs have been applied in various therapeutic methods against gliomas, including radiotherapy, PDT, photothermal therapy (PTT), and immunotherapy. Among them, radiotherapy plays a cornerstone role in cancer treatment,¹⁶³ which is one of the mainstays of glioma treatment.¹⁶⁴ Imaging, an integral part of radiotherapy, facilitates the depiction of targeted tumor sub-volumes, thereby accurately determining the uniform therapeutic dose in the target area. However, current clinical imaging techniques do not adequately meet the requirements for timely and targeted assessment of radiotherapy.¹⁶³ One type of NPs, composed of lipids and NFs, offers enhanced tumor imaging visualization, minimal systemic toxicity, and improved PDT efficacy. Owing to their intrinsic fluorescence imaging ability, the NPs demonstrate an excellent potential for targeted tumor sub-volume imaging, with fluorescence imaging revealing that the nanoparticles accumulate at the tumor site within 2 hours of injection and remain there for at least 48 hours, which provides a favorable tool for radiotherapy imaging, suggesting the potential application of NFs in radiotherapy imaging.¹⁶⁵

Nanofibers in Immunotherapy for Gliomas

It is well known that immunotherapy has been considered effective in inhibiting cancer metastasis and recurrence validly. An in situ-formed immunotherapeutic NF loaded with anti-CD47 antibodies can not only remove H⁺ produced after surgery, but also release the anti-CD47 antibody which effectively induces the host's innate and adaptive immune systems, promoting effective antigen presentation by macrophages and initiating a T-cell-mediated immune response to inhibit the growth of cancer cells, thereby inhibiting tumor recurrence and metastasis post-surgery,¹⁶⁶ further highlighting the potential of NFs in immunotherapy. Meanwhile, due to its advantages of regional selectivity, minimal toxicity, negligible invasiveness, short therapeutic duration, and repeatable treatments, nanofiber phototherapy has demonstrated excellent potential as a great approach for oncotherapy.¹⁶⁷

Nanofibers in Combination Therapy for Gliomas

NFs can also be an excellent platform for combination therapy of several therapeutic modules to synergistically combat gliomas. Among these, phototherapy is one of the representative therapeutic methods to combine with.^{168,169} NFs with hypoxia and a single-linear oxygen response that were designed to improve cellular uptake, drug release and co-delivery of photosensitizers and chemotherapeutic agents. The dual-responsive NFs not only increase the targeted concentration but also promote the release of photosensitizers and chemotherapeutic agents, which enhances the combination of photodynamic and chemotherapeutic treatments. The photosensitizer induced PDT, and the resulting hypoxic environment activated the chemotherapeutic drug precursors to achieve effective chemotherapy, thus inducing a synergistic therapeutic effect of photodynamic and chemotherapeutic therapy for gliomas.¹⁷⁰ Photopolymerized NFs can provide sustained local TMZ delivery. Significantly lower tumor weights were observed in photopolymerized NFs-treated mice, and higher apoptosis of GBM cells was also observed, without inducing brain cell death or activating microglia in mice. The study demonstrated that the combination of phototherapy and chemotherapy enhances anti-glioma efficacy, suggesting the great potential of photopolymerized NFs in GBM treatment.¹⁷¹ In another similar study, supramolecular micelles presented improved cellular uptake, negligible toxic and side effects and good biocompatibility, and increased the efficiency of intracellular ROS generation. In vivo evaluation indicated a synergistic therapeutic effect between PDT and hypoxia-activated chemotherapy. This study offers a special nanoplatform for the synergistic of PDT and chemotherapy, but also provides novel insights to design and develop multifunctional NDDS.¹⁷²

In addition, radiotherapy, chemotherapy, thermotherapy, and immunotherapy are also commonly used in combination therapy for glioma. Thermotherapy, a minimally invasive procedure, is well known as its medical application for the treatment of malignant brain tumors.¹⁷³ Silver NPs were designed to combine radiation and magnetic hyperthermia to treat human glioma U251 cells. The results showed that the NPs exhibited radiosensitivity and thermal sensitivity to U251 cells, enabling X-rays and heat to increase cellular uptake and promote apoptosis, significantly inhibiting the proliferation of glioma cells, suggesting the potential role of nanomaterials in efficiently killing glioma cells through the combination of radiotherapy and magnetic thermotherapy.¹⁷⁴ Multifunctional lipid magnetic nanocarriers can effectively accumulate at the tumor site after local administration without penetrating normal tissues, which can remarkably inhibit tumor invasion and proliferation and significantly prolong the survival of nude mice, demonstrating that multifunctional nanoplateforms provides a powerful and synergistic approach to the effective treatment of gliomas.¹⁷⁵ Moreover, radiotherapy is a mainstay method utilized clinically for local therapy.¹⁷⁶ A new microenvironment-responsive micelle was developed to target radiotherapy sensitizers and chemotherapeutic agents to GBM. Synergistically, radiotherapy led to high levels of apoptosis and DNA damage, and chemotherapeutic agents accumulated in large quantities at the tumor site, thereby notably reducing cell viability and proliferation in U251 cells, suggesting that NFs create a potential platform to enhance the sensitivity of radiotherapy and chemotherapy providing a novel strategy for overcoming the intrinsic therapeutic challenges of aggressive GBM.¹⁷⁷ In another study, a self-assembling nanofiber vaccine that forms nanofibrous structures around tumor cells, thereby capturing and encapsulating the autologous antigens maked by radiation, thereby effectively increasing cross-presentation by antigen-presenting cells and antigen involvement in lymph nodes. Compared to radiotherapy alone, the combination of nanovaccine and radiation therapy prominently improved therapeutic efficacy against 4T1 tumors, presenting a promising Therapeutic strategy for glioma radioimmunotherapy.¹⁷⁸

Taken together, nanomaterials have been widely used in multiple applications of gliomas, demonstrating tremendous superiority in eliminating gliomas and enhancing cancer treatment through functionalities such as magnetic thermotherapy, targeted drug delivery, and other diagnostic and therapeutic tools,⁹¹ indicating great potential for glioma applications. In pre-or clinical applications, future research directions could focus on developing NFs as a multifunctional platform for glioma combination therapies aiming to improve antitumor efficacy, minimize toxic and side effects, prolong patient survival, and reduce patient suffering.

The Protein Corona: Potential Side Effects of Nanofibers in Glioma Research

The understanding of nanomaterials is limited regarding their applications, particularly neglecting the interactions between biological systems and nanomaterials. Although many nanomaterials have been designed for disease diagnosis and treatment, the presence of nanomedicine in clinical practice remains rare.¹⁷⁹ Additionally, very few nanomaterials are currently approved by the Food and Drug Administration (FDA) for clinical use.¹⁸⁰ The main obstacle to the development of nanoformulations is the PC, which forms through the spontaneous absorption of protein onto nanomedicines when they are placed in biological fluid.^{37,181}

PC modifies the essential physicochemical properties of the nanomaterial surface, changing their size, biodistribution, stability, and safety.¹⁸² Meanwhile, the structure and conformation of proteins will be affected by the nanomaterials depending on their size, hydrophobicity, surface charge, and interaction time.^{183,184} Past research indicated that PC blocks the targeted delivery of nanomedicines to the therapeutic site¹⁸⁵ which allowed the nanomedicines to be quickly eliminated, simultaneously inducing an inflammatory response, thereby reducing their curative effect.^{186,187} Nevertheless, the latest research suggests that PC-nanomaterial interactions enhance the cell targeting and the uptake of therapeutic agents while reducing the unexpected cytotoxicity of nanomaterials.¹⁸³ It may be possible to obtain favorable nanomaterials for treatment by controlling their geometric shapes and surface properties to be compatible with desired proteins (Figure 5). For example, the selective antiproliferative effect of SnO₂ NPs¹⁸⁸ and Co₃O₄ NPs¹⁸⁹ on leukemia K562 cells may be related to their interaction with human serum albumin.

NFs are one of the most common nanomaterials, and some studies suggested that NFs may have the greatest impact on PC formation. One study demonstrated that titanium dioxide (TiO₂) NFs showed the highest protein adsorption

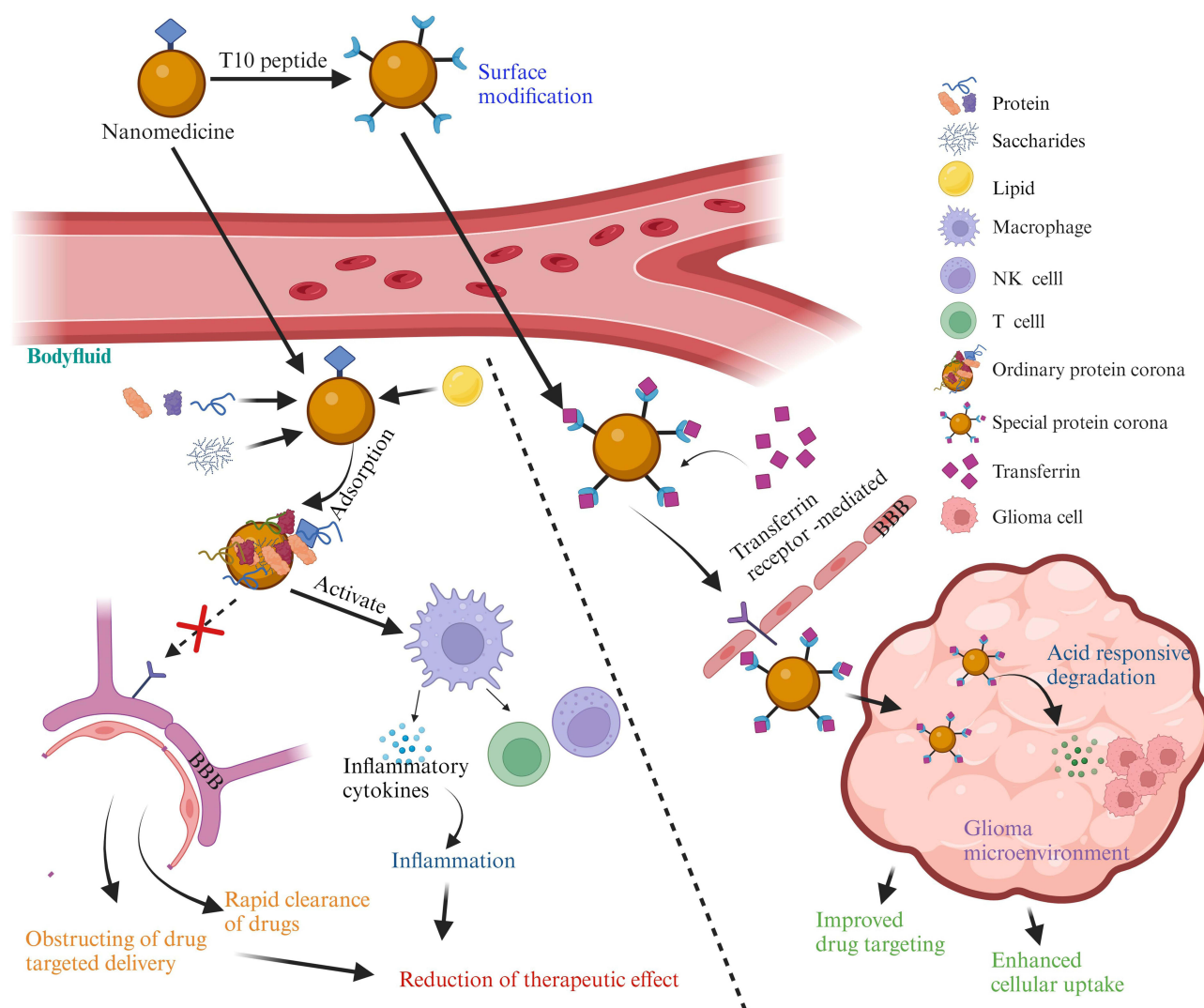


Figure 5 Reasonable utilization of protein Corona to improve drug efficacy. Protein corona is formed by spontaneous adsorption of protein onto nanomedicines when nanomedicines are placed in biological fluid, which demonstrates the disadvantages of blocking the targeted delivery of nanomedicines to the therapeutic site and simultaneously inducing inflammatory response, thereby reducing curative effects; and the advantages of enhancing the cell targeting and the therapeutic agent uptake while reducing the unexpected cytotoxicity of nanomaterials. Created in BioRender. Zhou, (S) (2025) <https://BioRender.com/z74c725>.

ability, induced the maximum cellular changes and had the greatest impact on DNA, proteins, and lipids among TiO₂ NPs, silicon dioxide (SiO₂) NPs, and indium tin oxide (ITO) NPs.¹⁹⁰ Plasmaized PCL NFs presented the power to absorb the nine best proteins, which are essential mediators of ECM interactions, which illustrates their significance for cell proliferation and viability.¹⁹¹ Because NFs are common carriers of glioma chemotherapeutic agents, PC has become a potential factor affecting the efficacy of glioma therapy. For instance, one recent study showed that the PC adsorption and aggregation were higher with the increase of drug-loading content so that the uptake of nanomedicine in U87MG cells decreased, resulting in insufficient drug concentration.¹⁹² However, another study showed that hollow covalent organic framework (COF) NFs spheres with high crystallinity and uniform size were used for non-interfering targeted drug delivery to gliomas based on their surface modification T10 peptide which can mediate transferrin (Tf) PC formation, significantly enabling them across the blood-brain barrier, improving therapeutic outcomes, prolonging median survival time, and reducing side effects.¹⁹³ In short, we can learn that the interaction between PC and NFs is not entirely unhelpful, but provides a new research hotspot for controlling the formation of PC to achieve the desired therapeutic effect through modulation of NF's surface properties. To make NFs more available for glioma clinical treatment, their interactions with PC should be taken into consideration. However, there are fewer studies on the

interaction of NFs with PCs, and the data reproducibility is one of the great challenges in the research process. Moreover, PC is the main cause of potential side effects of NFs. PC not only blocks the targeted delivery of nanomedicines to the therapeutic site allowing the nanomedicines to be quickly erased, but simultaneously induces inflammatory response, thereby reducing their curative effect.¹⁹⁴ The formation mechanisms of PC, the interaction between PC and nanomedicines still remains unclear which required further exploration in the future. These studies reveal that PC is not merely a source of toxic side effects but can also serve as a special tool to enhance nanomedicine targeting and absorption. The surface structure of PC is complicated and flexible due to the adsorption multiple substances like proteins, lipids, sugars, nucleic acids, etc, resulting in different effects on nanomedicines, which reduces the therapeutic efficacy to varying degrees.¹⁸⁶ Future research hotspots can focus on exploring the mechanisms of rapid drug clearance and inflammatory response caused by PC, thus reducing the side effects of nanomedicines in glioma therapy. Furthermore, it is worthwhile to explore the properties of PC surface structures that bind specific small molecules to improve the targeted delivery of nanomedicines. It is a promising strategy to search for potential targets in GME, which can be selectively bound to PC, so that the targeted transportation ability and absorption level of nanomedicines will be greatly increased, which not only improves the therapeutic efficacy of nanomedicines, but also reduces their toxic and side effects. For instance, the protein corona effect may be mitigated by modifying surface with PEG or employing biomimetic material coating like cell membranes to reduce PC formation, improving dimensions and morphology of NFs like shorter NFs diminishing the PC formation and decorating specific proteins to create a protective layer to decrease the adsorption of non-specific proteins.¹⁹⁵ Unfortunately, there is a dearth of relevant research.

Another issue is that data reproducibility has become an urgent need. Currently, in vitro cell models are used to explore the interaction between nanomedicines and proteins. Circular dichroism and surface-enhanced Raman scattering technology are favored techniques for studying protein conformational changes.¹⁹⁶ But both these techniques are difficult in detecting the conformational changes of diverse proteins. Data-driven models are currently the most successful computational approaches for predicting changes in NP surface characteristics and protein conformation. However, the universality of nanomaterial characteristics and the variability of the biological environment makes the basic dataset for modeling purposes impractical.¹⁹⁷ Although exploring the interactions between nanomaterials and proteins has become a new research trend, their interactions have rarely been considered, especially in clinical studies. Therefore, it is essential to explore new methods to study the changes on the surface structure of PC to overcome obstacles to the clinical use of nanomedicines.

Table 4 The Clinical Trials of Nanofiber-Based Formulations for Cancer Therapy

Formulation	Combination Therapy	Indication	Phase Stage	Status	Conclusion	ID/Refs
AGuIX	TMZ	GBM	Phase I; Phase 2	Active	NA	NCT04881032
MTX110	Gadoteridol	DIPG	Phase I; Phase 2	Completed	MTX110 showed better therapeutic effects while being tolerated by patients.	[194]
AGuIX	Radiotherapy	Brain metastases	Phase I	Completed	AGuIX combined with radiotherapy is safe and feasible for patients with brain metastases, specifically targeting brain metastases and retaining them in the tumor for one week.	[196]
AGuIX	Single agent	Brain metastases	Phase 2	Completed	AGuIX can accumulate in brain metastases with quantifiable uptake under radiotherapy.	[197]
NU-0129	Single agent	GBM, GS	Phase 0	Completed	The results showed that NU-0129 served as a potential brain-penetrant precision medicine approach for the systemic treatment of GBM.	[198]
nal-IRI	TMZ	GBM	Phase I	Completed	The results demonstrated that the dose-limiting toxicities of nal-IRI were diarrhea and neutropenia.	[199]

Abbreviations: CED, convection-enhanced delivery; DIPG, diffuse intrinsic pontine glioma; DMGs, diffuse midline gliomas; GBM, glioblastoma; nal-IRI, nanoliposomal irinotecan; TMZ, Temozolomide.

Discussion and Future Remarks

On average, 13 nanomedicines have been approved for clinical indications per 5 years since the mid-1990s.¹⁸⁰ Among these, various glioma cell-based nanomaterial formulations have been evaluated in clinical trials (Table 4). Emerging clinical trials have shown that nanomedicines have the ability to enhance anti-tumor effects and reducing toxic and side effects. A clinical trial showed that the nanomedicine, MTX110 exhibited superior efficacy while being tolerated by patients.¹⁹⁸ Another clinical trial indicated that AGuIX combined with radiotherapy was not only safe and feasible, but also targeted brain metastasis with sustained drug release.^{199,200} In one Phase 0 clinical trial, the results showed that NU-0129 served as a potential brain-penetrant precision medicine approach for the systemic treatment of GBM.²⁰¹ But in another Phase 1 clinical trial, nal-IRI showed the dose-limited toxicities mainly in diarrhea and neutropenia.²⁰² The degradation products of specific synthetic polymers (eg, PLA, PGA) may exhibit acidic characteristics, potentially inducing inflammatory responses. The certain long-term implanted NFs could cause immune reactions. The organic solvents employed in electrospinning may retain residual toxicity, adversely impacting cell viability and tissue regeneration. These deficiencies may be mitigated by utilizing materials with superior biocompatibility like collagen, chitosan, and PCL, preparing nanofiber solutions with non-toxic solvents like water or low-toxicity alternatives such as acetic acid, and implementing functional modifications to reduce immune responses, which can significantly enhance the overall performance and safety of the NFs.^{203,204} The preclinical clinical trials have confirmed the great potential of nano-formulations in glioma therapies, but current clinical trials are insufficient to support broader clinical application of nano-formulations. Additionally, there are many known and unknown adverse effects of nano-formulations that need to be addressed; therefore, more clinical trials are needed to continue the discussion regarding glioma treatment and its associated potential risks in order to prepare for the nanomedicines to be ready for clinical indications.

NFs provide a broad research platform for glioma studies in DDS, which can be multifunctionalized by combining them with multiple components. To date, NFs can be combined with various materials to form multifunctional compliant nanomaterials, hormones;²⁰⁵ chitosan;²⁰⁶ graphene;²⁰⁷ cyclodextrin;²⁰⁸ α -Mangostin;²⁰⁹ bacterial cellulose;²¹⁰ peptide;⁸⁹ folic acid;²¹¹ bioactive compounds such as essential oils and plant extracts; chemical compounds like porphyrin²¹² and manganese dioxide;²¹³ chemical elements like selenium;²¹⁴ etc. For instance, a multifunctional nanocarrier was endowed with the capability of PDT induced by targeted X-ray and chemotherapy boosted by cascaded ROS, breaking from the traditional view of NFs as drug carriers only, and discovering the potential of NFs to be applied in other anticancer therapies.²¹⁵ Furthermore, composite NFs incorporating spiropyran can control C6 glioma cancer cell adhesion and detachment by changing UV and visible light irradiation while exhibiting significant biocompatibility and negligible toxicity to C6 glioma cancer cells, indicating a promising substrate for glioma cell research.¹²¹ Nevertheless, the current research focuses on certain individual substances that can enhance or increase the functionality of NFs, and there are no reports of systematic and comprehensive statistics or classification of such substances.

And then, the adjustable size and diameter of NFs empower them with multiple functions and their potential of greatly exerting value, which contributing to their applications in biomedicine.²¹⁶ One study stated that the improved biological, therapeutic and toxicological properties of an ultra-small (<8 nm) silica NP-DOX conjugate were significantly better than those of the native drug after intravenous injection, which was not only cleared by the kidneys, but also effective in treating two different clinically relevant models of high-grade gliomas.²¹⁷ Moreover, small-sized NFs were more concentrated at the glioma site than the large one, and the gliomas were more sensitive to small-sized NFs.²¹⁸ However, another experiment showed that neuron growth and migration could be differentiated by fiber diameter. NFs showed negative effects on neurite extension and Schwann cell migration, thus NFs diameters and spaces between NFs should be taken into consideration when constructing nanofiber structures to fabricate expected GME models.²¹⁹ However, there are limited studies on such issues, which are insufficient to support their application. Further research directions could focus on optimizing NFs.

In addition, the large-scale production of NFs and the toxicity generated during the production process is still potential problem that currently threaten the use of NFs in clinical applications. The harmful effects of common solvents during NFs synthesis limits the application of NFs in both clinical and commercial environments, making it necessary to discover new synthesis processes to reduce their toxicity and to enable their large-scale production for

commercialization.²²⁰ Moreover, there is a lack of uniform quality control standards for nanofiber formulations, which also needs further exploration.

Due to its excellent biocompatibility, biodegradability and 3D structure similar to ECM, hydrogel NFs have been widely used in biomedical field.²²¹ In regenerative medicine, a magnetic nanofiber hydrogel produced to promote peripheral nerve regeneration, demonstrated its ability to improve recovery of the myelin sheath nerve in rats, and degradation within one week without immediate inflammatory reaction, exhibiting the meaningful potential of nanofiber hydrogel to regenerate peripheral nerves.²²² Moreover, hydrogel NFs show great advantages in tumor application. A novel 3D nanofiber-based hydrogel composite endowed with comparable degradability and mechanical properties to tumor tissues has the function of mimicking the natural ECM. The incorporated NFs enhance the hydrogel's mechanical properties, allowing for various fiber densities to match the multiple elastic modulus of different tumor tissues. Moreover, the scaffold's degradability provides ample space for tumor cell secretion and ECM remodeling. Through the assessment of cancer stem cell marker expression, it was confirmed that prostate cancer cells develop invasive and metastatic phenotypes within 3D scaffolds, indicating that the 3D scaffold tumor models can successfully simulate the TME and possess significant potential in developing effective targeted agents.²²³ Hydrogel NFs are also excellent carriers for drug delivery owing to their self-healing properties, injectability and pH responsiveness. One nanofiber-based hydrogel composite displayed not only the excellent biocompatibility and degradability *in vivo* and *in vitro*, but the efficient anti-tumor ability via continuous release of DOX without significant systemic toxicity, suggesting their huge potential value in anti-tumor treatment.²²¹ Hydrogels, as novel nano-material, have emerged as a potential candidate for glioma treatment, which has been widely used in the management of brain tumors. Hydrogel NDDS shows excellent therapeutic effects in glioma treatment through various response modes, including pH-response, temperature-response, light-response, liposome-response, ROS response, and enzyme response.²²⁴ A temperature-response hydrogel loaded with docetaxel (DTX) exhibited higher effect in killing U87MG cells compared with free DTX. The *in vivo* experimental results demonstrated that the hydrogel could consistently release DTX under various pH conditions for over one month, displaying an excellent tumor inhibitory effect, thereby highlighting its potential in glioma treatment.²²⁵ To sum up, hydrogel NFs not only have the ability to mimic the GME, but also act as useful carriers for targeting glioma therapeutic drugs, revealing the great potential of hydrogel NFs in gliomas treatments. However, there are currently fewer studies on the application of hydrogel NFs in gliomas, and the potential side effect of hydrogel NFs still remains unclear. There is no doubt that hydrogel NFs serve as an excellent platform for enhancing research in glioma therapy. Future research could focus on the application of hydrogel NFs in gliomas and investigate their potential toxicity to enhance or develop novel glioma therapies.

Electrospinning has emerged as the most promising technique for producing NFs. Especially, nanofiber-based DDS have demonstrated significant application potential in glioma treatment, yet still facing numerous challenges. *In vivo* models are constrained by the BBB, immune responses and inflammatory reactions, resulting in lower drug efficacy compared with *in vitro* models, thereby obstructing the clinical application of NFs. Moreover, electrospun NFs often lack active targeting capabilities, leading to inadequate drug accumulation at the tumor site.^{226,227} While self-assembled NFs can achieve molecular-level targeting, they suffer from relatively low stability and drug-loading capacity.⁵⁶ Therefore, it is crucial to develop 3D tumor models that more closely replicate the *in vivo* environment for preliminary nanofiber screening. Additionally, multifunctional NFs can be engineered by integrating targeted ligands (eg, peptides and antibodies) and stimuli-responsive materials (eg, pH-sensitive polymers) to enhance targeting efficiency. Alternatively, combining NFs with other nanotechnologies, such as liposomes and nanoparticles, to form composite delivery systems may improve BBB penetration. However, such studies remain limited and warrant further exploration.

Conclusion

NFs are widely used in glioma applications. NDDS is undoubtedly an excellent platform for delivering chemotherapeutic drugs such as TMZ, which can bypass the BBB in several ways, so that the agents can achieve the effective concentration at the tumor site, enhancing the chemotherapy efficacy while reducing the systemic side effects. And the controlled release of the nanomedicines after the surgery can effectively prevent the recurrence of gliomas. Aligned NFs share similar structure and physicochemical properties with the brain ECM, which mimics the TME to explore mechanisms

related to glioma cell migration and thus discover new therapeutic targets. A large number of nanoscaffolds have been used to mimic the TME to study glioma cell migration and infiltration as well as to facilitate drug screening. Moreover, NFs are now widely used in glioma applications such as radiotherapy, phototherapy, thermotherapy and immunotherapy. Nevertheless, the NDDS is still in the process of continuous optimization. Various methods have shown better results such as adding new components to nanocarriers to expand or enhance their functions, or improving their functions by adjusting their size and diameter, but these studies are still relatively few and lack a comprehensive and systematic data to support the clinical application of nanocarriers. Although electrospinning technology is the most promising method for producing NFs, there are also many challenges. Additionally, PC, a primary cause of NFs' side effects, can obstruct drug transport, accelerate drug clearance, and cause inflammatory response, and another study showed that PC enhanced the targeting and increased cellular uptake of nanomedicines. However, there is a lack of additional clinical studies to elucidate the interaction of PC with NFs. More research is needed to fully understand these interactions, focusing on overcoming the side effects of PC.

Abbreviations

3D, three-dimensional; Ace-DEX, acetalated dextran; ALP, alkaline phosphatase; BBB, blood-brain barrier; BCNC, bacterial cellulose nano-crystal; BCNU, carmustine; CAD, computer-aided design; CB, cisplatin; CED, convection-enhanced delivery; CNS, central nervous system; CNF, carbon nanofibers; COF, covalent organic framework; C-PCL, chitosan-polycaprolactone; CS, chitosan; CT, computed tomography; CUR, curcumin; CW, carmustine wafers; DA, dopamine; DDS, drug delivery systems; DIPG, diffuse intrinsic pontine glioma; DMGs, diffuse midline gliomas; DOX, Doxorubicin; DTIC, dacarbazine; DTX, docetaxel; ECM, extracellular matrix; FDA, Food and Drug Administration; GBM, glioblastoma; Gel, gelatin; GIC, glioblastoma initiating cells; GME, glioma microenvironment; GPX4, glutathione peroxidase 4; GT, gelatin; HA, hyaluronic acid; HSNM, hybrid-structured nanofibrous membrane; ITO, indium tin oxide; LMP, lysosomal membrane permeability; NA, not applicable; nal-IRI, nanoliposomal irinotecan; NDDS, nanodrug delivery system; NFP, peptide nanofiber precursor; NFS, nanofiber system; NFs, nanofibers; NPs, nanoparticles; OL, Oleuropein; PAN, polyacrylonitrile; PANi, polyaniline; PC, protein corona; PCL, poly(ϵ -caprolactone); PDT, photodynamic therapy; PEDOT, shell/core poly(3,4-ethylenedioxythiophene); PTT, photothermal therapy; PEO, polyethylene oxide; P-gp, P-glycoprotein; PLA, polylactic acid; PPy, polypyrrole; PS, polystyrene; PTX, paclitaxel; PVA, polyvinyl alcohol; PVC, poly(vinyl chloride); PVDF, poly(vinylidene fluoride); ROS, reactive oxygen species; SiO₂, silicon dioxide; Tf, transferrin; TiO₂, titanium dioxide; TME, tumor microenvironment; TMZ, temozolomide.

Data Sharing Statement

No primary research results, software or code have been included and no new data were generated or analyzed as part of this review.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that this paper was conducted without any financial or business relationship that could be considered as a potential conflict of interest. Graphical abstract *Created in BioRender: Zhou, S. (2025) <https://BioRender.com/u94n318>*.

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