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REVIEW

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

Shangjun Zhou[1,2,*], Mingcheng Zhang[3,*], Jiayu Wang[2], Xi Chen[2], Zhijie Xu[4], Yuanliang Yan[2,5], Yong Li[1]

[1]Department of Pediatric Surgery, Hunan Children's Hospital, Changsha, Hunan, People's Republic of China; [2]Department of Pharmacy, Xiangya Hospital, Central South University, Changsha, Hunan, People's Republic of China; [3]Center of Endoscopy, The Second Affiliated Hospital of Shandong First Medical University Tai'an, Shandong, People's Republic of China; [4]Department of Pathology, Xiangya Hospital, Central South University, Changsha, Hunan, People's Republic of China; [5]National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, Changsha, Hunan, People's Republic of China

*These authors contributed equally to this work

Correspondence: Yuanliang Yan, Department of Pharmacy, Xiangya Hospital, Central South University, Changsha, Hunan, People's Republic of China, Email yanyuanliang@csu.edu.cn; Yong Li, Department of Pediatric Surgery, Hunan Children's Hospital, Changsha, Hunan, People's Republic of China, Email liyongpuwaike@163.com

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

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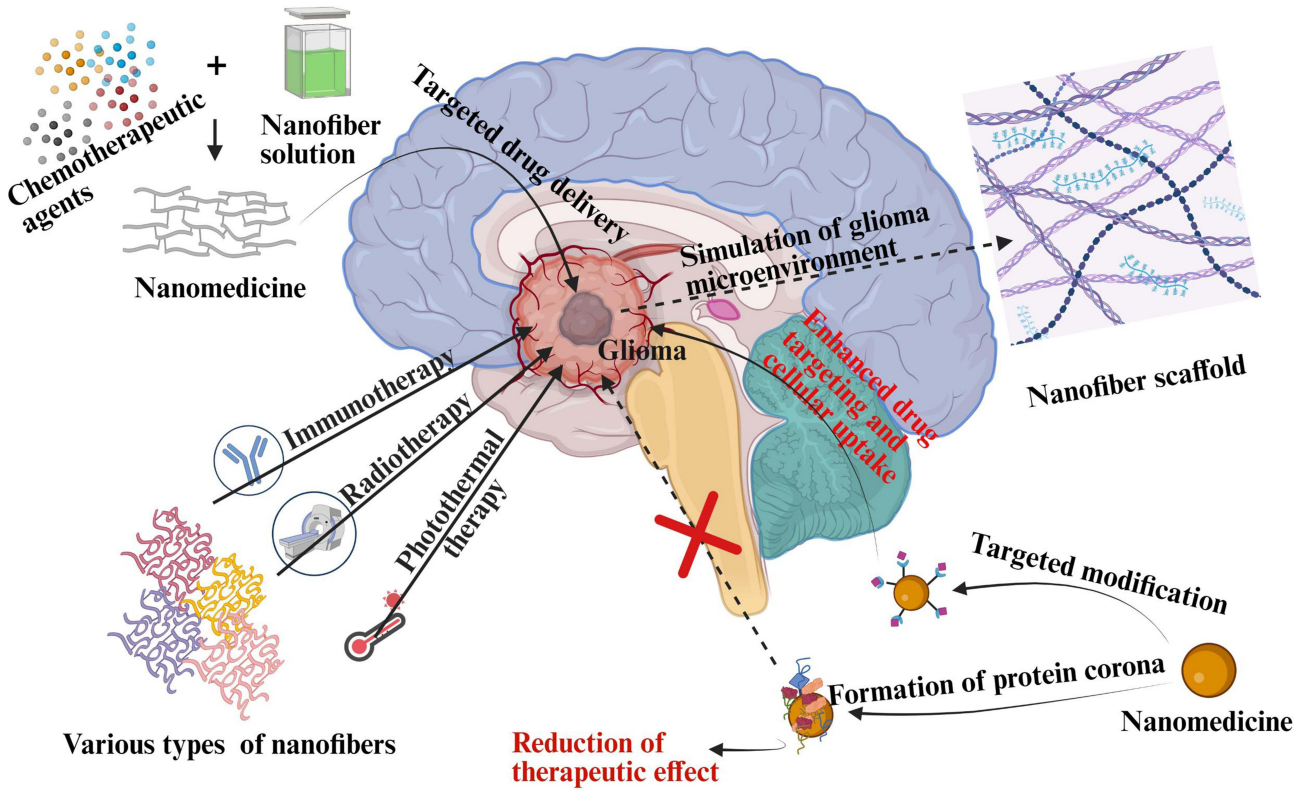
Graphical Abstract



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 applications[24] 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 efficiency[30] 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 al[38] 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

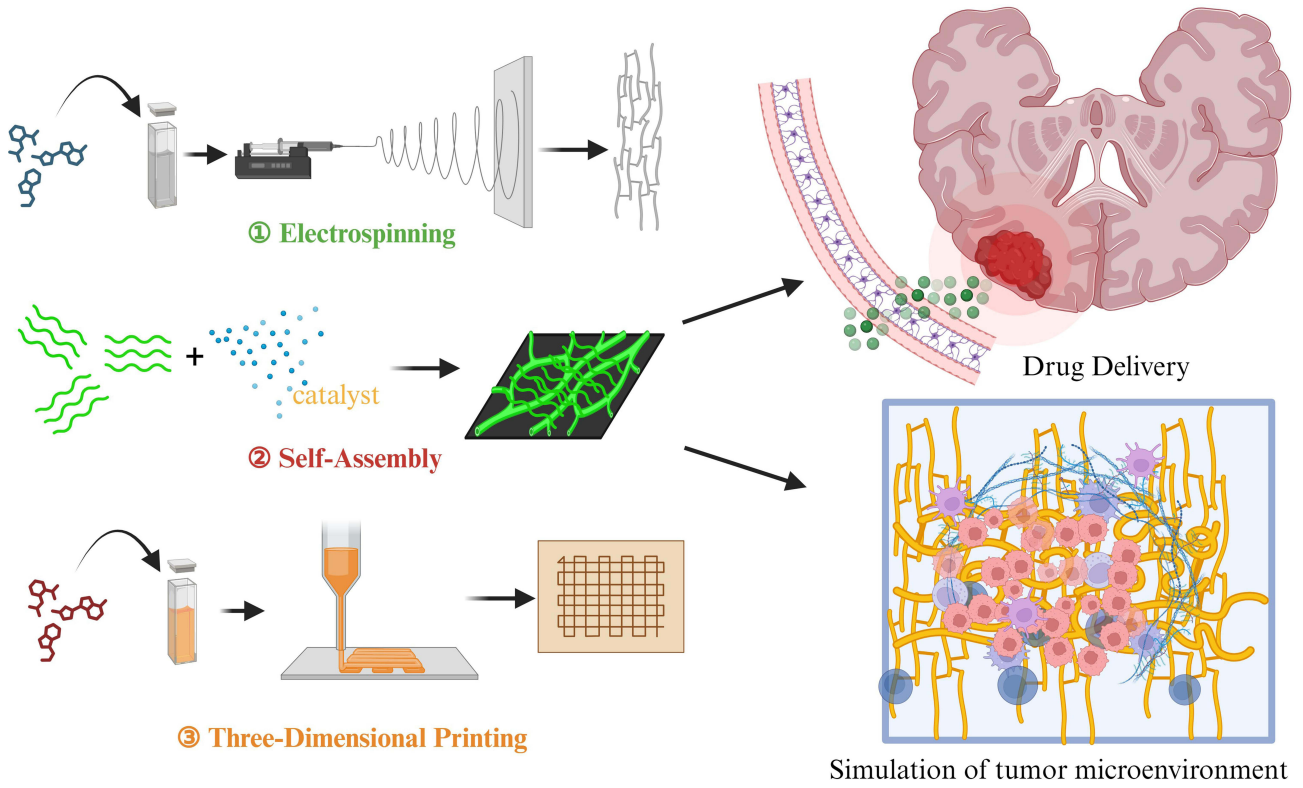


Figure 1 The synthesis and application of nanofibers in gliomas. Nanofibers are typically synthesized through electrospinning, self-assembly, and three-dimensional printing for drug delivery and microenvironment simulation of gliomas *Created in BioRender. Zhou, (S) (2025)* https://BioRender.com/r41m582.

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	1mL/h	26kV	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 poly3,4-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 recurrence[54] (Figure 2). Electrospun nanofiber scaffolds

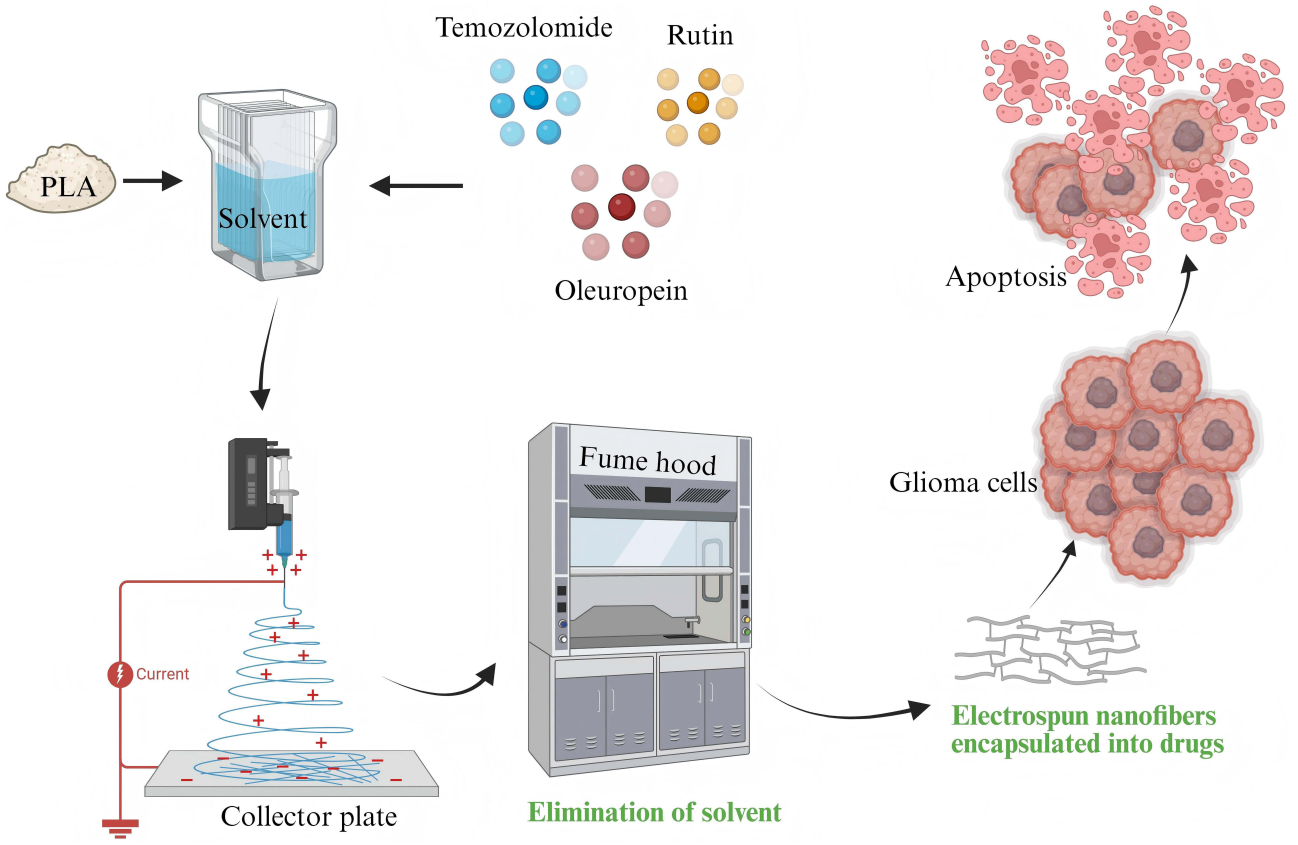


Figure 2 Effective application of nanofiber drug delivery system in glioma treatment. Through electrospinning technology, Temozolomide, Oleuropein or rutin were encapsulated within nanofibers, followed by solvent evaporation in a fume hood. These drug-loaded nanofibers were subsequently applied to treat glioma cells, inducing significant apoptosis in the targeted cell population. *Created in BioRender. Zhou, (S) (2025)* https://BioRender.com/s19j395.

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 tools[89] and biomarker detection[90]), 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 al[99] 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 μm, 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

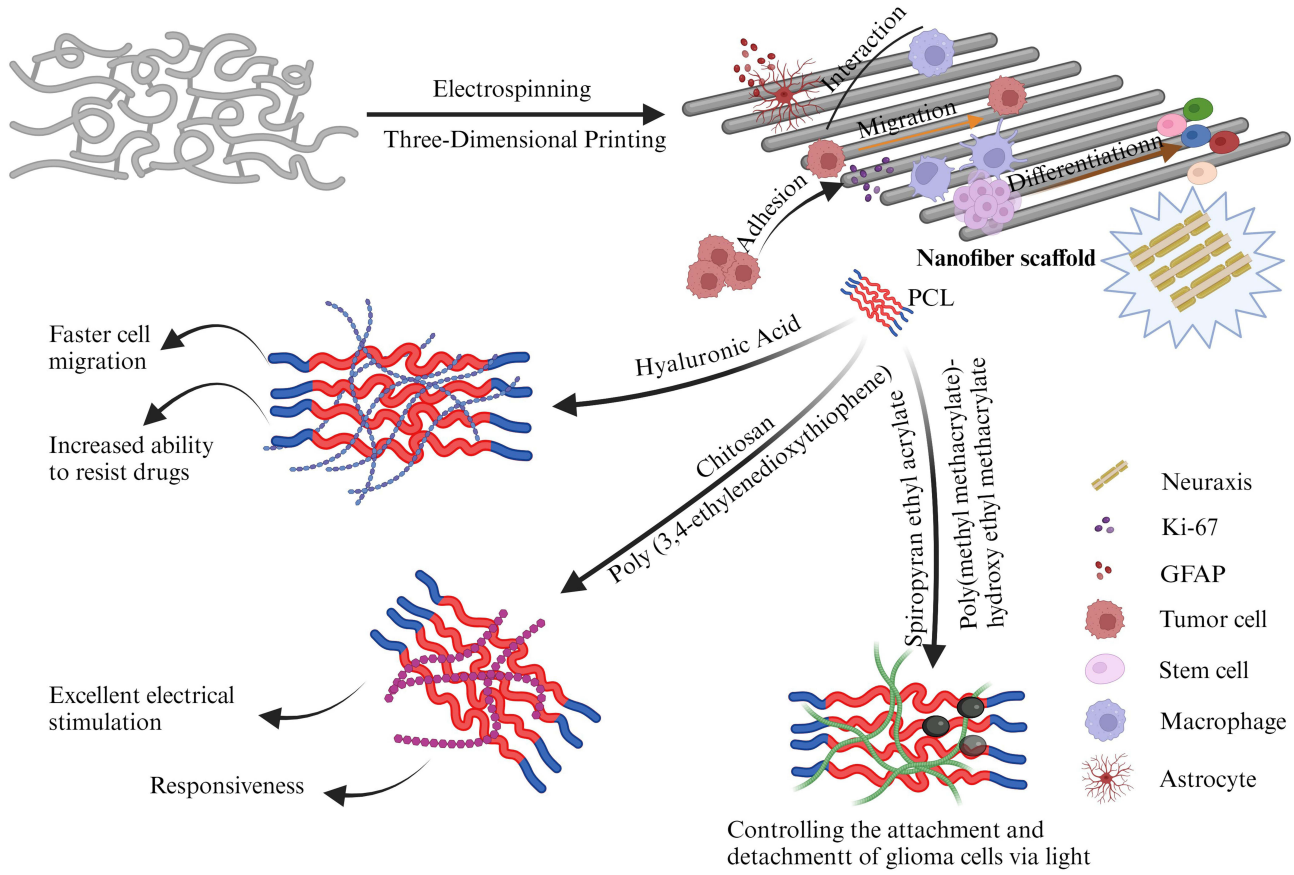


Figure 3 Nanofiber in simulation of glioma microenvironment. The nanofiber scaffold supports the growth and migration of glioma cells as well as cell interactions. By adding different components to the scaffold, the functionality of the nanofiber scaffold can be further optimized *Created in BioRender.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

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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 release[126](Table 2), and improvement of the physicochemical and pharmacokinetic properties of drugs[127] (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 BBB[136] 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 ± 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 sulfde) 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 permeability[150] 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]

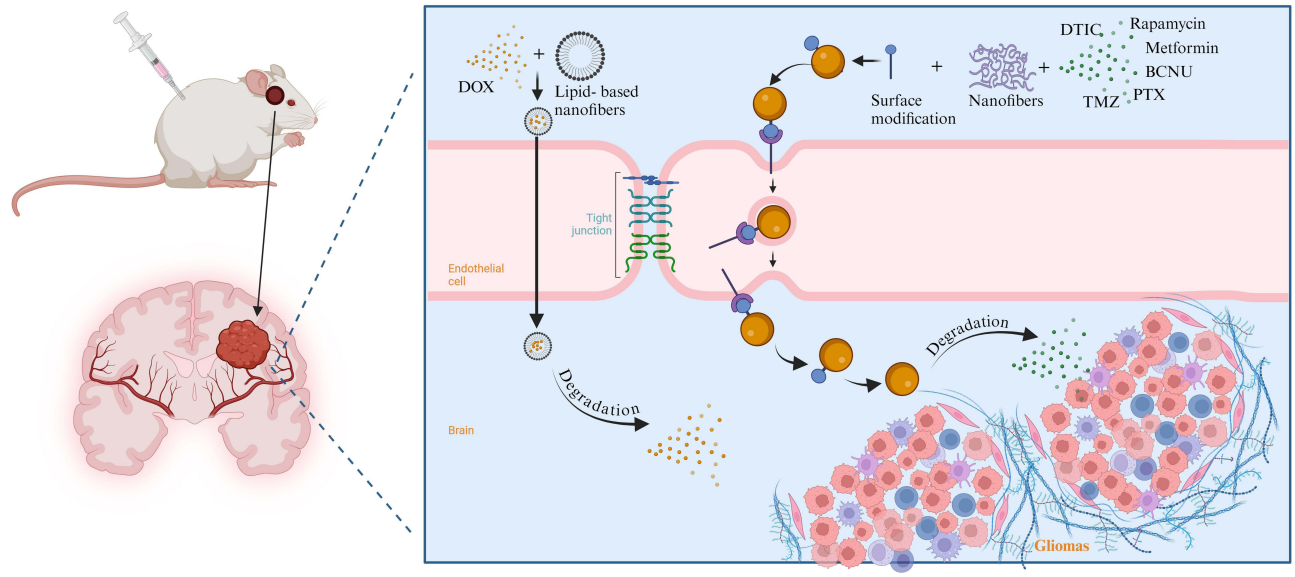

Figure 4 The way of nanomedicine crossing the blood-brain barrier. After entering the systemic circulation, nanomedicine can cross the blood-brain barrier via surface modification and target the tumor site, and then showing sustained drug release through slow degradation achieving anti glioma effect 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 gliomas[154](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 nanoplatforms 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 site[185] 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 NPs[188] and Co3O4 NPs[189] 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

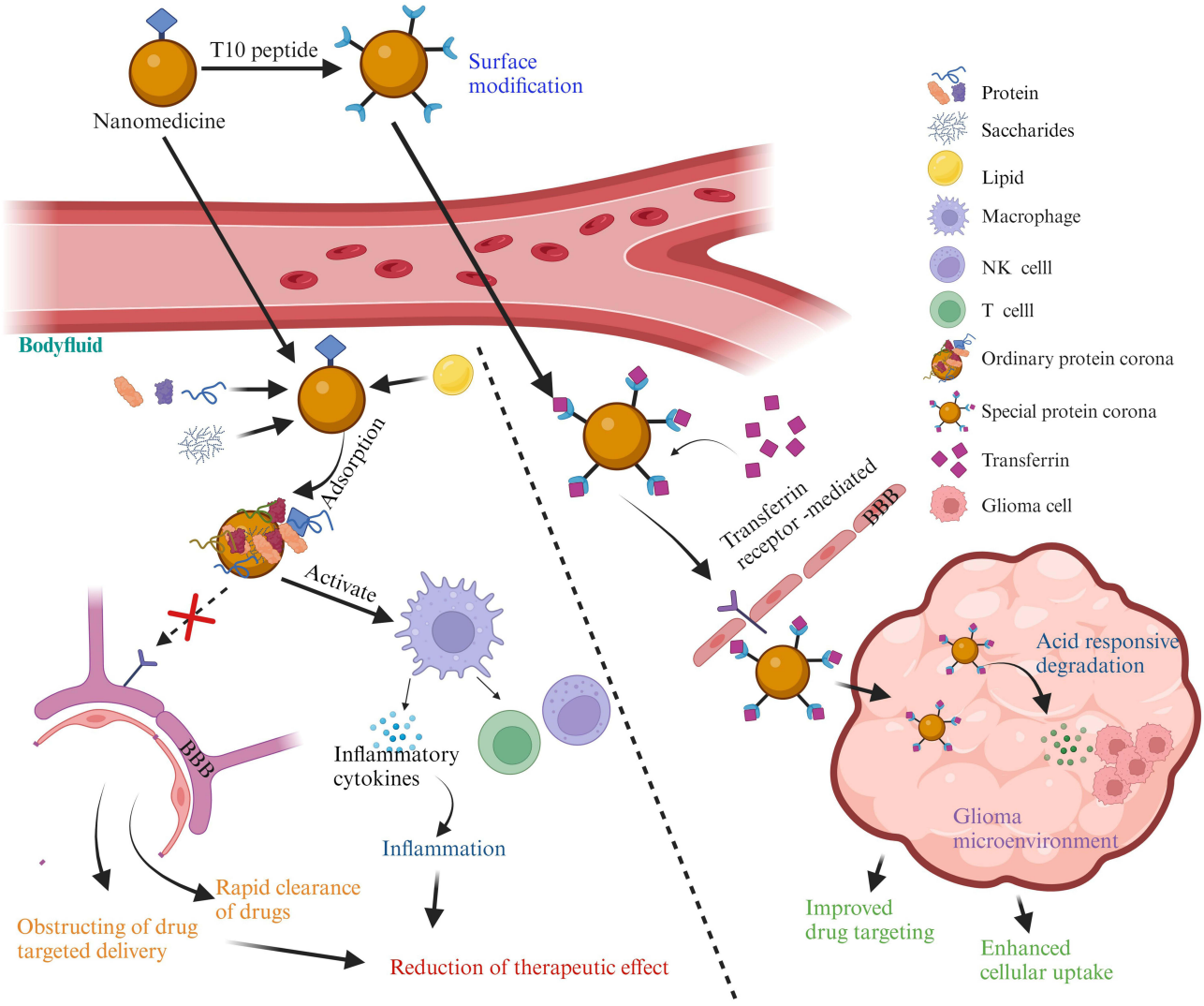

Figure 5 Reasonable utilization of protein Corona to improve drug efficacy. Protein corona is formed by spontaneous absorption of protein onto nanomedicines when nanomedicines are placed in biological fluid, which demonstrates the disadvantages of blocking the targeted delivery of nanomedicines to the 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

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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	Phase1; Phase 2	Active	NA	NCT04881032
MTX110	Gadoteridol	DIPG	Phase 1; Phase 2	Completed	MTX110 showed better therapeutic effects while being tolerated by patients.	[194]
AGuIX	Radiotherapy	Brain metastases	Phase 1	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 1	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 porphyrin[212] 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 for 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 poly3,4-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

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References

1. Feng S, Liu H, Dong X, Du P, Guo H, Pang Q. Identification and validation of an autophagy-related signature for predicting survival in lower-grade glioma. *Bioengineered*. 2021;12(2):9692–9708. doi:10.1080/21655979.2021.1985818
2. Chen R, Smith-Cohn M, Cohen AL, Colman H. Glioma subclassifications and their clinical significance. *Neurotherapeutics*. 2017;14 (2):284–297. doi:10.1007/s13311-017-0519-x
3. Sampson JH, Maus MV, June CH. Immunotherapy for brain tumors. *J Clin Oncol*. 2017;35(21):2450–2456. doi:10.1200/JCO.2017.72.8089
4. Garcia-Garcia E, Andrieux K, Gil S, Couvreur P. Colloidal carriers and blood-brain barrier (BBB) translocation: a way to deliver drugs to the brain? *Int J Pharm*. 2005;298(2):274–292. doi:10.1016/j.ijpharm.2005.03.031
5. Nicholson JG, Fine HA. Diffuse Glioma Heterogeneity and Its Therapeutic Implications. *Cancer Discov*. 2021;11(3):575–590. doi:10.1158/2159-8290.CD-20-1474
6. Tseng -Y-Y, Chen T-Y, Liu S-J. Role of polymeric local drug delivery in multimodal treatment of malignant glioma: a review. *Int J Nanomed*. 2021;16:4597–4614. doi:10.2147/IJN.S309937
7. Liu Z, Zhang W, Cheng X, et al. Overexpressed XRCC2 as an independent risk factor for poor prognosis in glioma patients. *Mol Med*. 2021;27 (1):52. doi:10.1186/s10020-021-00316-0
8. Chintagumpala M, Gajjar A. Brain tumors. *Pediatr Clin North Am*. 2015;62(1):167–178. doi:10.1016/j.pcl.2014.09.011
9. Norouzi M. Recent advances in brain tumor therapy: application of electrospun nanofibers. *Drug Discov Today*. 2018;23(4):912–919. doi:10.1016/j.drudis.2018.02.007
10. Ahmed R, Oborski MJ, Hwang M, Lieberman FS, Mountz JM. Malignant gliomas: current perspectives in diagnosis, treatment, and early response assessment using advanced quantitative imaging methods. *Cancer Manag Res*. 2014;6:149–170. doi:10.2147/CMAR.S54726
11. Huang D, Lin C, Wen X, Gu S, Zhao P. A potential nanofiber membrane device for filling surgical residual cavity to prevent glioma recurrence and improve local neural tissue reconstruction. *PLoS One*. 2016;11(8):e0161435. doi:10.1371/journal.pone.0161435
12. Weller M, Wick W, Aldape K, et al. Glioma. *Nat Rev Dis Primers*. 2015;1:15017. doi:10.1038/nrdp.2015.17
13. Tseng -Y-Y, Kau Y-C, Liu S-J. Advanced interstitial chemotherapy for treating malignant glioma. *Expert Opin Drug Deliv*. 2016;13 (11):1533–1544. doi:10.1080/17425247.2016.1193153
14. Tseng -Y-Y, Wang Y-C, Su C-H, et al. Concurrent delivery of carmustine, irinotecan, and cisplatin to the cerebral cavity using biodegradable nanofibers: in vitro and in vivo studies. *Colloids Surf B Biointerfaces*. 2015;134:254–261. doi:10.1016/j.colsurfb.2015.06.055
15. Beliveau A, Thomas G, Gong J, Wen Q, Jain A. Aligned nanotopography promotes a migratory state in glioblastoma multiforme tumor cells. *Sci Rep*. 2016;6:26143. doi:10.1038/srep26143
16. Farshbaf M, Mojarad-Jabali S, Hemmati S, et al. Enhanced BBB and BBTB penetration and improved anti-glioma behavior of Bortezomib through dual-targeting nanostructured lipid carriers. *J Control Release*. 2022;345:371–384. doi:10.1016/j.jconrel.2022.03.019
17. Lang F, Liu Y, Chou FJ, Yang C. Genotoxic therapy and resistance mechanism in gliomas. *Pharmacol Ther*. 2021;228:107922. doi:10.1016/j.pharmthera.2021.107922
18. Li H, Chen L, Li -J-J, et al. miR-519a enhances chemosensitivity and promotes autophagy in glioblastoma by targeting STAT3/Bcl2 signaling pathway. *J Hematolo Oncol*. 2018;11:70. doi:10.1186/s13045-018-0618-0
19. Zhang -S-S, Li R-Q, Chen Z, Wang X-Y, Dumont AS, Fan X. Immune cells: potential carriers or agents for drug delivery to the central nervous system. *Mil Med Res*. 2024;11(1):19. doi:10.1186/s40779-024-00521-y
20. Zhang Y-Q, Guo -R-R, Chen Y-H, et al. Ionizable drug delivery systems for efficient and selective gene therapy. *Mil Med Res*. 2023;10(1):9. doi:10.1186/s40779-023-00445-z
21. Huang W-Q, Zhu Y-Q, You W, et al. Tumor microenvironment triggered the synthesis of an excellent sonosensitizer in tumor for sonodynamic therapy. *ACS Appl Mater Interfaces*. 2022. doi:10.1021/acsami.2c05369
22. Xun Y, Yang H, Kaminska B, You H. Toll-like receptors and toll-like receptor-targeted immunotherapy against glioma. *J Hematol Oncol*. 2021;14(1):176. doi:10.1186/s13045-021-01191-2
23. Guo Q-L, Dai X-L, Yin M-Y, et al. Nanosensitizers for sonodynamic therapy for glioblastoma multiforme: current progress and future perspectives. *Mil Med Res*. 2022;9(1):26. doi:10.1186/s40779-022-00386-z
24. Reddy VS, Tian Y, Zhang C, et al. A review on electrospun nanofibers based advanced applications: from health care to energy devices. *Polymers*. 2021;13(21):3746. doi:10.3390/polym13213746
25. Sun Y, Lyu B, Yang C, et al. An enzyme-responsive and transformable PD-L1 blocking peptide-photosensitizer conjugate enables efficient photothermal immunotherapy for breast cancer. *Bioact Mater*. 2023;22:47–59. doi:10.1016/j.bioactmat.2022.08.020
26. Hu -J-J, Lin N, Zhang Y, Xia F, Lou X. Nanofibers in organelles: from structure design to biomedical applications. *Angew Chem Int Ed Engl*. 2024;63(5):e202313139. doi:10.1002/anie.202313139
27. Maleki H, Khoshnevisan K, Sajjadi-Jazi SM, et al. Nanofiber-based systems intended for diabetes. *J Nanobiotechnol*. 2021;19(1):317. doi:10.1186/s12951-021-01065-2
28. Boda SK, Almoshari Y, Wang H, et al. Mineralized nanofiber segments coupled with calcium-binding BMP-2 peptides for alveolar bone regeneration. *Acta Biomater*. 2019;85:282–293. doi:10.1016/j.actbio.2018.12.051
29. Pandey G, Phatale V, Khairnar P, et al. Supramolecular self-assembled peptide-engineered nanofibers: a propitious proposition for cancer therapy. *Int J Biol Macromol*. 2024;256(Pt 2):128452. doi:10.1016/j.ijbiomac.2023.128452
30. Mundargi RC, Babu VR, Rangaswamy V, Patel P, Aminabhavi TM. Nano/micro technologies for delivering macromolecular therapeutics using poly(D,L-lactide-co-glycolide) and its derivatives. *J Control Release*. 2008;125(3):193–209. doi:10.1016/j.jconrel.2007.09.013
31. Bastiancich C, Danhier P, Préat V, Danhier F. Anticancer drug-loaded hydrogels as drug delivery systems for the local treatment of glioblastoma. *J Control Release*. 2016;243:29–42. doi:10.1016/j.jconrel.2016.09.034
32. Lin F-W, Chen P-Y, Wei K-C, Huang C-Y, Wang C-K, Yang H-W. Rapid in situ MRI traceable gel-forming dual-drug delivery for synergistic therapy of brain tumor. *Theranostics*. 2017;7(9):2524–2536. doi:10.7150/thno.19856
33. Liu Y, Chen X, Lin X, et al. Electrospun multi-chamber core-shell nanofibers and their controlled release behaviors: a review. *Wiley Interdisciplinary Rev Nanomed Nanobiotechnol*. 2024;16(2):e1954. doi:10.1002/wnan.1954

34. Barbu E, Molnàr E, Tsibouklis J, Górecki DC. The potential for nanoparticle-based drug delivery to the brain: overcoming the blood-brain barrier. *Expert Opin Drug Deliv*. 2009;6(6):553–565. doi:10.1517/17425240902939143
35. Min S, Yu Q, Ye J, et al. Nanomaterials with glucose oxidase-mimicking activity for biomedical applications. *Molecules*. 2023;28(12):4615. doi:10.3390/molecules28124615
36. Eygeris Y, Gupta M, Kim J, Sahay G. Chemistry of lipid nanoparticles for RNA delivery. *Acc Chem Res*. 2022;55(1):2–12. doi:10.1021/acs.accounts.1c00544
37. Mahmoudi M, Landry MP, Moore A, Coreas R. The protein Corona from nanomedicine to environmental science. *Nat Rev Mater*. 2023;8(7):422–438. doi:10.1038/s41578-023-00552-2
38. Nasir A, Khan A, Li J, et al. Nanotechnology, A tool for diagnostics and treatment of cancer. *Curr Top Med Chem*. 2021;21(15):1360–1376. doi:10.2174/1568026621666210701144124
39. Khodadadi M, Alijani S, Montazeri M, Esmaeilizadeh N, Sadeghi-Soureh S, Pilehvar-Soltanahmadi Y. Recent advances in electrospun nanofiber-mediated drug delivery strategies for localized cancer chemotherapy. *J Biomed Mater Res A*. 2020;108(7):1444–1458. doi:10.1002/jbm.a.36912
40. Kievit FM, Cooper A, Jana S, et al. Aligned chitosan-polycaprolactone polyblend nanofibers promote the migration of glioblastoma cells. *Adv Healthc Mater*. 2013;2(12):1651–1659. doi:10.1002/adhm.201300092
41. Modeling tumor microenvironments using custom-designed biomaterial scaffolds. 2016.
42. All-Fiber Structured Electronic Skin with High Elasticity and Breathability. 2019.
43. Xue J, Wu T, Dai Y, Xia Y. Electrospinning and electrospun nanofibers: methods, materials, and applications. *Chem Rev*. 2019;119(8):5298–5415. doi:10.1021/acs.chemrev.8b00593
44. Yen S-C, Liu Z-W, Juang R-S, et al. Carbon nanotube/conducting polymer hybrid nanofibers as novel organic bioelectronic interfaces for efficient removal of protein-bound uremic toxins. *ACS Appl Mater Interfaces*. 2019;11(47):43843–43856. doi:10.1021/acsami.9b14351
45. Obeid AT, Garcia LHA, TRdL N, et al. Effects of hybrid inorganic-organic nanofibers on the properties of enamel resin infiltrants - An in vitro study. *J Mech Behav Biomed Mater*. 2022;126:105067. doi:10.1016/j.jmbbm.2021.105067
46. Wang Y, Cui W, Chou J, Wen S, Sun Y, Zhang H. Electrospun nanosilicates-based organic/inorganic nanofibers for potential bone tissue engineering. *Colloids Surf B Biointerfaces*. 2018;172:90–97. doi:10.1016/j.colsurfb.2018.08.032
47. Mirdailami O, Soleimani M, Dinarvand R, et al. Controlled release of rhEGF and rhbFGF from electrospun scaffolds for skin regeneration. *J Biomed Mater Res A*. 2015;103(10):3374–3385. doi:10.1002/jbm.a.35479
48. Norouzi M, Shabani I, Ahvaz HH, Soleimani M. PLGA/gelatin hybrid nanofibrous scaffolds encapsulating EGF for skin regeneration. *J Biomed Mater Res A*. 2015;103(7):2225–2235. doi:10.1002/jbm.a.35355
49. Gomes MR, Castelo Ferreira F, Sanjuan-Alberte P. Electrospun piezoelectric scaffolds for cardiac tissue engineering. *Biomater Adv*. 2022;137:212808. doi:10.1016/j.bioadv.2022.212808
50. Jarak I, Silva I, Domingues C, Santos AI, Veiga F, Figueiras A. Nanofiber carriers of therapeutic load: current trends. *Int J Mol Sci*. 2022;23(15):8581. doi:10.3390/ijms23158581
51. Steffi C, Wang D, Kong CH, et al. Estradiol-loaded Poly(ε-caprolactone)/Silk Fibroin electrospun microfibers decrease osteoclast activity and retain osteoblast function. *ACS Appl Mater Interfaces*. 2018;10(12):9988–9998. doi:10.1021/acsami.8b01855
52. Conductive polymer ultrafine fibers via electrospinning: preparation, physical properties and applications. 2020.
53. Temperature effects on electrospun chitosan nanofibers. 2020.
54. Ercelik M, Tekin C, Parin FN, et al. Co-loading of temozolomide with oleuropein or rutin into polylactic acid core-shell nanofiber webs inhibit glioblastoma cell by controlled release. *Int J Biol Macromol*. 2023;253(Pt 2):126722. doi:10.1016/j.ijbiomac.2023.126722
55. Wang H, Feng Z, Xu B. Intercellular instructed-assembly mimics protein dynamics to induce cell spheroids. *J Am Chem Soc*. 2019;141(18):7271–7274. doi:10.1021/jacs.9b03346
56. Karavasili C, Panteris E, Vizirianakis IS, Koutsopoulos S, Fatouros DG. Chemotherapeutic delivery from a self-assembling peptide nanofiber hydrogel for the management of glioblastoma. *Pharm Res*. 2018;35(8):166.
57. Yu G-F, Yan X, Yu M, et al. Patterned, highly stretchable and conductive nanofibrous PANI/PVDF strain sensors based on electrospinning and in situ polymerization. *Nanoscale*. 2016;8(5):2944–2950. doi:10.1039/C5NR08618C
58. Shahriar SMS, Mondal J, Hasan MN, Revuri V, Lee DY, Lee YK. Electrospinning nanofibers for therapeutics delivery. *Nanomaterials*. 2019;9(4):532. doi:10.3390/nano9040532
59. Chen Z, Chen Z, Zhang A, Hu J, Wang X, Yang Z. Electrospun nanofibers for cancer diagnosis and therapy. *Biomater Sci*. 2016;4(6):922–932. doi:10.1039/c6bm00070c
60. Zhang Z, Liu S, Xiong H, et al. Electrospun PLA/MWCNTs composite nanofibers for combined chemo- and photothermal therapy. *Acta Biomaterialia*. 2015;26:115–123. doi:10.1016/j.actbio.2015.08.003
61. Bending instability of electrically charged liquid jets of polymer solutions in electrospinning. 2000.
62. Emulsion electrospinning: fundamentals, food applications and prospects. 2018.
63. Refate A, Mohamed Y, Mohamed M, et al. Influence of electrospinning parameters on biopolymers nanofibers, with emphasis on cellulose & chitosan. *Heliyon*. 2023;9(6):e17051. doi:10.1016/j.heliyon.2023.e17051
64. Yoon J, Yang HS, Lee BS, Yu WR. Recent progress in coaxial electrospinning: new parameters, various structures, and wide applications. *Adv Mater*. 2018;30(42):e1704765. doi:10.1002/adma.201704765
65. Norouzi MR, Ghasemi-Mobarakeh L, Itel F, et al. Emulsion electrospinning of sodium alginate/poly(ε-caprolactone) core/shell nanofibers for biomedical applications. *Nanoscale Adv*. 2022;4(13):2929–2941. doi:10.1039/D2NA00201A
66. Graham-Gurysh EG, Moore KM, Schorzman AN, et al. Tumor responsive and tunable polymeric platform for optimized delivery of paclitaxel to treat glioblastoma. *ACS Appl Mater Interfaces*. 2020;12(17):19345–19356. doi:10.1021/acsami.0c04102
67. Du L, Li T, Jin F, et al. Design of high conductive and piezoelectric poly (3,4-ethylenedioxythiophene)/chitosan nanofibers for enhancing cellular electrical stimulation. *J Colloid Interface Sci*. 2020;559:65–75. doi:10.1016/j.jcis.2019.10.003
68. Unal S, Arslan S, Karademir Yilmaz B, Kazan D, Oktar FN, Gunduz O. Glioblastoma cell adhesion properties through bacterial cellulose nanocrystals in polycaprolactone/gelatin electrospun nanofibers. *Carbohydr Polym*. 2020;233:115820. doi:10.1016/j.carbpol.2019.115820

69. Rolandi M, Rolandi R. Self-assembled chitin nanofibers and applications. *Adv Colloid Interface Sci*. 2014;207:216–222. doi:10.1016/j.cis.2014.01.019
70. Kang HJ, Chen N, Dash BC, Hsia HC, Berthiaume F. Self-assembled nanomaterials for chronic skin wound healing. *Adv Wound Care*. 2021;10(5):221–233. doi:10.1089/wound.2019.1077
71. La Manna S, Di Natale C, Onesto V, Marasco D. Self-assembling peptides: from design to biomedical applications. *International Journal of Molecular Sciences*. 2021;22(23):12662. doi:10.3390/ijms222312662
72. Zhang P, Cheetham AG, Lin Y-A, Cui H. Self-assembled Tat nanofibers as effective drug carrier and transporter. *ACS Nano*. 2013;7(7):5965–5977. doi:10.1021/nn401667z
73. Wang L, Lv Y, Li C, et al. Transformable dual-inhibition system effectively suppresses renal cancer metastasis through blocking endothelial cells and cancer stem cells. *Small*. 2020;16(40):e2004548. doi:10.1002/smll.202004548
74. Liu N, Zhu L, Li Z, Liu W, Sun M, Zhou Z. In situ self-assembled peptide nanofibers for cancer theranostics. *Biomater Sci*. 2021;9(16):5427–5436.
75. Wang Z, Wang Y, Yan J, et al. Pharmaceutical electrospinning and 3D printing scaffold design for bone regeneration. *Advanced Drug Delivery Reviews*. 2021;174:504–534.
76. Salehi S, Ghomi H, Hassanzadeh-Tabrizi SA, Koupaei N, Khodaei M. Antibacterial and osteogenic properties of chitosan-polyethylene glycol nanofibre-coated 3D printed scaffold with vancomycin and insulin-like growth factor-1 release for bone repair. *Int J Biol Macromol*. 2025;298:139883. doi:10.1016/j.ijbiomac.2025.139883
77. Levato R, Jungst T, Scheuring RG, Blunk T, Groll J, Malda J. From shape to function: the next step in bioprinting. *Adv Mater*. 2020;32(12):e1906423. doi:10.1002/adma.201906423
78. Houshyar S, Pillai MM, Saha T, et al. Three-dimensional directional nerve guide conduits fabricated by dopamine-functionalized conductive carbon nanofibre-based nanocomposite ink printing. *RSC Adv*. 2020;10(66):40351–40364. doi:10.1039/D0RA06556K
79. Behera S, Mohapatra S, Behera BC, Thatoi H, Gao W. Recent updates on green synthesis of lignin nanoparticle and its potential applications in modern biotechnology. *Crit Rev Biotechnol*. 2023;43:1–21. doi:10.1080/07388551.2021.2003292
80. Choi C, Yun E, Cha C. Emerging technology of nanofiber-composite hydrogels for biomedical applications. *Macromol Biosci*. 2023;23:e2300222. doi:10.1002/mabi.202300222
81. Ibrahim MA, Alhalafi MH, Emam EM, Ibrahim H, Mosaad RM. A Review of chitosan and chitosan nanofiber: preparation, characterization, and its potential applications. *Polymers*. 2023;15(13):1.
82. Jiang Z, Zheng Z, Yu S, et al. Nanofiber scaffolds as drug delivery systems promoting wound healing. *Pharmaceutics*. 2023;15(7):1.
83. Chen K, Li Y, Li Y, et al. Stimuli-responsive electrospun nanofibers for drug delivery, cancer therapy, wound dressing, and tissue engineering. *J Nanobiotechnol*. 2023;21(1):237. doi:10.1186/s12951-023-01987-z
84. Tomar Y, Pandit N, Priya S, Singhvi G. Evolving trends in nanofibers for topical delivery of therapeutics in skin disorders. *ACS Omega*. 2023;8(21):18340–18357.
85. Anani OA, Adama KK, Ukhurebor KE, Habib AI, Abanihi VK, Pal K. Application of nanofibrous protein for the purification of contaminated water as a next generational sorption technology: a review. *Nanotechnology*. 2023;34(23):232004. doi:10.1088/1361-6528/acbd9f
86. Saravanakumar K, Park S, Santosh SS, et al. Application of hyaluronic acid in tissue engineering, regenerative medicine, and nanomedicine: a review. *Int J Biol Macromol*. 2022;222(Pt B):2744–2760. doi:10.1016/j.ijbiomac.2022.10.055
87. Ansari MA. Nanotechnology in food and plant science: challenges and future prospects. *Plants*. 2023;12(13). doi:10.3390/plants12132565
88. Abadi B, Goshtasbi N, Bolourian S, Tahsili J, Adeli-Sardou M, Forootanfar H. Electrospun hybrid nanofibers: fabrication, characterization, and biomedical applications. *Front Bioeng Biotechnol*. 2022;10:986975. doi:10.3389/fbioe.2022.986975
89. Liu Y, Xing R, Li J, Yan X. Covalently triggered self-assembly of peptide-based nanodrugs for cancer theranostics. *iScience*. 2023;26(1):105789. doi:10.1016/j.isci.2022.105789
90. Nene A, Geng S, Zhou W, Yu XF, Luo H, Ramakrishna S. Black phosphorous aptamer-based platform for biomarker detection. *Curr Med Chem*. 2023;30(8):935–952. doi:10.2174/0929867329666220225110302
91. Mamun A, Sabantina L. Electrospun magnetic nanofiber mats for magnetic hyperthermia in cancer treatment applications-technology, mechanism, and materials. *Polymers*. 2023;15(8):1902. doi:10.3390/polym15081902
92. Zaszczyńska A, Niemczyk-Soczynska B, Sajkiewicz P. A comprehensive review of electrospun fibers, 3d-printed scaffolds, and hydrogels for cancer therapies. *Polymers*. 2022;14(23):5278. doi:10.3390/polym14235278
93. Erickson A, Chiarelli PA, Huang J, Levengood SL, Zhang M. Electrospun nanofibers for 3-D cancer models, diagnostics, and therapy. *Nanoscale Horiz*. 2022;7(11):1279–1298. doi:10.1039/D2NH00328G
94. Cho K, Wang X, Nie S, Chen ZG, Shin DM. Therapeutic nanoparticles for drug delivery in cancer. *Clin Cancer Res*. 2008;14(5):1310–1316. doi:10.1158/1078-0432.CCR-07-1441
95. Rahman MA, Shin DM. CCR 20th anniversary commentary: prospects and challenges of therapeutic nanoparticles in cancer. *Clin Cancer Res*. 2015;21(20):4499–4501. doi:10.1158/1078-0432.CCR-14-3126
96. Dadwal A, Baldi A, Kumar Narang R. Nanoparticles as carriers for drug delivery in cancer. *Artif Cells Nanomed Biotechnol*. 2018;46(sup2):295–305. doi:10.1080/21691401.2018.1457039
97. Zhu Y, Jia J, Zhao G, et al. Multi-responsive nanofibers composite gel for local drug delivery to inhibit recurrence of glioma after operation. *J Nanobiotechnol*. 2021;19(1):198. doi:10.1186/s12951-021-00943-z
98. Saleh A, Marhuenda E, Fabre C, et al. A novel 3D nanofibre scaffold conserves the plasticity of glioblastoma stem cell invasion by regulating galectin-3 and integrin-β1 expression. *Sci Rep*. 2019;9(1):14612. doi:10.1038/s41598-019-51108-w
99. Marhuenda E, Fabre C, Zhang C, et al. Glioma stem cells invasive phenotype at optimal stiffness is driven by MGAT5 dependent mechanosensing. *J Exp Clin Cancer Res*. 2021;40(1):139. doi:10.1186/s13046-021-01925-7
100. Wang Q, Hu B, Hu X, et al. Tumor evolution of glioma-intrinsic gene expression subtypes associates with immunological changes in the microenvironment. *Cancer Cell*. 2017;32(1):42–56.e6. doi:10.1016/j.ccell.2017.06.003
101. Da Ros M, De Gregorio V, Iorio AL, et al. Glioblastoma chemoresistance: the double play by microenvironment and blood-brain barrier. *Int J Mol Sci*. 2018;19(10):2879. doi:10.3390/ijms19102879

102. Jain A, Betancur M, Patel GD, et al. Guiding intracortical brain tumour cells to an extracortical cytotoxic hydrogel using aligned polymeric nanofibres. *Nat Mater*. 2014;13(3):308–316. doi:10.1038/nmat3878
103. Erickson A, Sun J, Levengood SKL, Zhang M. Hyaluronic Acid-Coated Aligned nanofibers for the promotion of glioblastoma migration. *ACS Appl Bio Mater*. 2019;2(3):1088–1097. doi:10.1021/acsabm.8b00704
104. Zhou H, Chen B, Zhang L, Li C. Machine learning-based identification of lower grade glioma stemness subtypes discriminates patient prognosis and drug response. *Comput Struct Biotechnol J*. 2023;21:3827–3840. doi:10.1016/j.csbj.2023.07.029
105. Wang S, Yan W, Kong L, et al. Oncolytic viruses engineered to enforce cholesterol efflux restore tumor-associated macrophage phagocytosis and anti-tumor immunity in glioblastoma. *Nat Commun*. 2023;14(1):4367. doi:10.1038/s41467-023-39683-z
106. Canella A, Nazzaro M, Rajendran S, et al. Genetically modified IL2 bone-marrow-derived myeloid cells reprogram the glioma immunosuppressive tumor microenvironment. *Cell Rep*. 2023;42(8):112891. doi:10.1016/j.celrep.2023.112891
107. Jahandideh A, Yarizadeh M, Noei-Khesht Masjedi M, et al. Macrophage's role in solid tumors: two edges of a sword. *Cancer Cell Int*. 2023;23(1):150. doi:10.1186/s12935-023-02999-3
108. Colen CB, Shen Y, Ghoddoussi F, et al. Metabolic targeting of lactate efflux by malignant glioma inhibits invasiveness and induces necrosis: an in vivo study. *Neoplasia*. 2011;13(7):620–632. doi:10.1593/neo.11134
109. Rao SS, Lannutti JJ, Viapiano MS, Sarkar A, Winter JO. Toward 3D biomimetic models to understand the behavior of glioblastoma multiforme cells. *Tissue Eng Part B Rev*. 2014;20(4):314–327. doi:10.1089/ten.teb.2013.0227
110. Koh I, Cha J, Park J, Choi J, Kang S-G, Kim P. The mode and dynamics of glioblastoma cell invasion into a decellularized tissue-derived extracellular matrix-based three-dimensional tumor model. *Sci Rep*. 2018;8(1):4608. doi:10.1038/s41598-018-22681-3
111. Stanković T, Randelović T, Dragoj M, et al. In vitro biomimetic models for glioblastoma-a promising tool for drug response studies. *Drug Resist Updat*. 2021;55:100753. doi:10.1016/j.drup.2021.100753
112. Puhl DL, Funnell JL, Nelson DW, Gottipati MK, Gilbert RJ. Electrospun fiber scaffolds for engineering glial cell behavior to promote neural regeneration. *Bioengineering*. 2020;8(1). doi:10.3390/bioengineering8010004
113. Johnson CD, Ar D, Puhl DL, Wich DM, Vesperman A, Gilbert RJ. Electrospun fiber surface nanotopography influences astrocyte-mediated neurite outgrowth. *Biomed Mater*. 2018;13(5):054101. doi:10.1088/1748-605X/aac4de
114. Guan Y, Ren Z, Yang B, et al. Dual-bionic regenerative microenvironment for peripheral nerve repair. *Bioactive Materials*. 2023;26:370–386. doi:10.1016/j.bioactmat.2023.02.002
115. Yim EKF, Darling EM, Kulangara K, Guilak F, Leong KW. Nanotopography-induced changes in focal adhesions, cytoskeletal organization, and mechanical properties of human mesenchymal stem cells. *Biomaterials*. 2010;31(6):1299–1306. doi:10.1016/j.biomaterials.2009.10.037
116. Kulangara K, Yang Y, Yang J, Leong KW. Nanotopography as modulator of human mesenchymal stem cell function. *Biomaterials*. 2012;33(20):4998–5003. doi:10.1016/j.biomaterials.2012.03.053
117. Teo BKK, Wong ST, Lim CK, et al. Nanotopography modulates mechanotransduction of stem cells and induces differentiation through focal adhesion kinase. *ACS Nano*. 2013;7(6):4785–4798. doi:10.1021/nn304966z
118. Johnson J, Nowicki MO, Lee CH, et al. Quantitative analysis of complex glioma cell migration on electrospun polycaprolactone using time-lapse microscopy. *Tissue Eng Part C Methods*. 2009;15(4):531–540. doi:10.1089/ten.tec.2008.0486
119. Rao SS, Nelson MT, Xue R, et al. Mimicking white matter tract topography using core-shell electrospun nanofibers to examine migration of malignant brain tumors. *Biomaterials*. 2013;34(21):5181–5190. doi:10.1016/j.biomaterials.2013.03.069
120. Grodecki J, Short AR, Winter JO, et al. Glioma-astrocyte interactions on white matter tract-mimetic aligned electrospun nanofibers. *Biotechnol Prog*. 2015;31(5):1406–1415. doi:10.1002/btpr.2123
121. Karimipour K, Keyvan Rad J, Shirvalilou S, Khoei S, Mahdavian AR. Spiropyran-based photoswitchable acrylic nanofibers: a stimuli-responsive substrate for light controlled C6 glioma cells attachment/detachment. *Colloids Surf B Biointerfaces*. 2021;203:111731. doi:10.1016/j.colsurfb.2021.111731
122. Johnson CDL, Zuidema JM, Kearns KR, et al. The effect of electrospun fiber diameter on astrocyte-mediated neurite guidance and protection. *ACS Appl Bio Mater*. 2019;2(1):104–117. doi:10.1021/acsabm.8b00432
123. Unal S, Arslan S, Yilmaz BK, et al. Polycaprolactone/gelatin/hyaluronic acid electrospun scaffolds to mimic glioblastoma extracellular matrix. *Materials*. 2020;13(11):2661. doi:10.3390/ma13112661
124. Cui Y, Lee P, Reardon JJ, et al. Evaluating glioblastoma tumour sphere growth and migration in interaction with astrocytes using 3D collagen-hyaluronic acid hydrogels. *J Mater Chem B*. 2023;11(24):5442–5459. doi:10.1039/D3TB00066D
125. Vishwanath K, Wilson B, Geetha KM, Murugan V. Polysorbate 80-coated albumin nanoparticles to deliver paclitaxel into the brain to treat glioma. *Ther Deliv*. 2023;14(3):193–206. doi:10.4155/tde-2022-0056
126. Li J, Liu Y, Abdelhakim HE. Drug delivery applications of coaxial electrospun nanofibres in cancer therapy. *Molecules*. 2022;27(6):1.
127. Kesharwani P, Kumari K, Gururani R, Jain S, Sharma S. Approaches to address PK-PD challenges of conventional liposome formulation with special reference to cancer, alzheimer's, diabetes, and glaucoma: an update on modified liposomal drug delivery system. *Curr Drug Metab*. 2022;23(9):678–692. doi:10.2174/1389200223666220609141459
128. Wu W, Klockow JL, Zhang M, et al. Glioblastoma multiforme (GBM): an overview of current therapies and mechanisms of resistance. *Pharmacol Res*. 2021;171:105780. doi:10.1016/j.phrs.2021.105780
129. Ou Z, Li X, You Y, Liu D, Wang J. Interpreting the therapeutic efficiency of multifunctional hybrid nanostructure against glioblastoma. *ACS Omega*. 2023;8(13):12259–12267. doi:10.1021/acsomega.2c08265
130. Farheen M, Akhter MH, Chitme H, Suliman M, Jaremko M, Emwas AH. Surface-modified biobased polymeric nanoparticles for dual delivery of doxorubicin and gefitinib in glioma cell lines. *ACS Omega*. 2023;8(31):28165–28184. doi:10.1021/acsomega.3c01375
131. Chowdhary SA, Ryken T, Newton HB. Survival outcomes and safety of carmustine wafers in the treatment of high-grade gliomas: a meta-analysis. *J Neurooncol*. 2015;122(2):367–382. doi:10.1007/s11060-015-1724-2
132. Ahmad S, Khan I, Pandit J, et al. Brain targeted delivery of carmustine using chitosan coated nanoparticles via nasal route for glioblastoma treatment. *Int J Biol Macromol*. 2022;221:435–445. doi:10.1016/j.ijbiomac.2022.08.210
133. Yi S, Yang F, Jie C, Zhang G. A novel strategy to the formulation of carmustine and bioactive nanoparticles co-loaded PLGA biocomposite spheres for targeting drug delivery to glioma treatment and nursing care. *Artif Cells Nanomed Biotechnol*. 2019;47(1):3438–3447. doi:10.1080/21691401.2019.1652628

134. Erthal LCS, Shi Y, Sweeney KJ, Gobbo OL, Ruiz-Hernandez E. Nanocomposite formulation for a sustained release of free drug and drug-loaded responsive nanoparticles: an approach for a local therapy of glioblastoma multiforme. *Sci Rep*. 2023;13(1):5094. doi:10.1038/s41598-023-32257-5
135. Fan CH, Liu WL, Cao H, Wen C, Chen L, Jiang G. O6-methylguanine DNA methyltransferase as a promising target for the treatment of temozolomide-resistant gliomas. *Cell Death Dis*. 2013;4(10):e876. doi:10.1038/cddis.2013.388
136. Salvatori L, Malatesta S, Illi B, et al. nitric oxide prevents glioblastoma stem cells' expansion and induces temozolomide sensitization. *Int J mol Sci*. 2023;24(14). doi:10.3390/ijms241411286
137. Fu D, Calvo JA, Samson LD. Balancing repair and tolerance of DNA damage caused by alkylating agents. *Nature Reviews Cancer*. 2012;12(2):104–120. doi:10.1038/nrc3185
138. Rezaee A, Tehrany PM, Tirabadi FJ, et al. Epigenetic regulation of temozolomide resistance in human cancers with an emphasis on brain tumors: function of non-coding RNAs. *Biomed Pharmacother*. 2023;165:115187. doi:10.1016/j.biopha.2023.115187
139. Dymova MA, Kuligina EV, Richter VA. Molecular mechanisms of drug resistance in glioblastoma. *Int J Mol Sci*. 2021;22(12):6385. doi:10.3390/ijms22126385
140. Liu S-J, Yang S-T, Chen S-M, et al. Novel multi-drugs incorporating hybrid-structured nanofibers enhance alkylating agent activity in malignant gliomas. *Ther Adv Med Oncol*. 2019;11:1758835919875555. doi:10.1177/1758835919875555
141. Ramachandran R, Junnuthula VR, Gowd GS, et al. Theranostic 3-dimensional nano brain-implant for prolonged and localized treatment of recurrent glioma. *Sci Rep*. 2017;7:43271. doi:10.1038/srep43271
142. Wang F, Porter M, Konstantopoulos A, Zhang P, Cui H. Preclinical development of drug delivery systems for paclitaxel-based cancer chemotherapy. *J Control Release*. 2017;267:100–118. doi:10.1016/j.jconrel.2017.09.026
143. Dmello C, Sonabend A, Arrieta VA, et al. Translocon-associated protein subunit SSR3 determines and predicts susceptibility to paclitaxel in breast cancer and glioblastoma. *Clin Cancer Res*. 2022;28(14):3156–3169. doi:10.1158/1078-0432.CCR-21-2563
144. Weaver BA. How Taxol/paclitaxel kills cancer cells. *Mol Biol Cell*. 2014;25(18):2677–2681. doi:10.1091/mbc.e14-04-0916
145. Das T, Anand U, Pandey SK, et al. Therapeutic strategies to overcome taxane resistance in cancer. *Drug Resist Updat*. 2021;55:100754. doi:10.1016/j.drup.2021.100754
146. Rizvi SFA, Abbas N, Zhang H, Fang Q. Identification of a pH-Responsive Peptide-Paclitaxel Conjugate as a Novel Drug with Improved Therapeutic Potential. *J Med Chem*. 2023;66(12):8324–8337. doi:10.1021/acs.jmedchem.3c00382
147. Chen H, Wen J. Iron oxide nanoparticles loaded with paclitaxel inhibits glioblastoma by enhancing autophagy-dependent ferroptosis pathway. *Eur J Pharmacol*. 2022;921:174860. doi:10.1016/j.ejphar.2022.174860
148. Bazzazzadeh A, Dizaji BF, Kianinejad N, Nouri A, Irani M. Fabrication of poly(acrylic acid) grafted-chitosan/polyurethane/magnetic MIL-53 metal organic framework composite core-shell nanofibers for co-delivery of temozolomide and paclitaxel against glioblastoma cancer cells. *Int J Pharm*. 2020;587:119674. doi:10.1016/j.ijpharm.2020.119674
149. Wiwatchaitawee K, Ebeid K, Quarterman JC, et al. Surface modification of nanoparticles enhances drug delivery to the brain and improves survival in a glioblastoma multiforme murine model. *Bioconjug Chem*. 2022;33(11):1957–1972. doi:10.1021/acs.bioconjchem.1c00479
150. Farheen M, Akhter MH, Chitme H, et al. Harnessing folate-functionalized nasal delivery of dox-erlo-loaded biopolymeric nanoparticles in cancer treatment: development, optimization, characterization, and biodistribution analysis. *Pharmaceuticals*. 2023;16(2). doi:10.3390/ph16020207
151. Du Y, Xia L, Jo A, et al. Synthesis and Evaluation of Doxorubicin-Loaded Gold Nanoparticles for Tumor-Targeted Drug Delivery. *Bioconjug Chem*. 2018;29(2):420–430. doi:10.1021/acs.bioconjchem.7b00756
152. Chibh S, Aggarwal N, Mallick Z, et al. Bio-piezoelectric phenylalanine-αβ-dehydrophenylalanine nanotubes as potential modalities for combinatorial electrochemotherapy in glioma cells. *Biomater Sci*. 2023;11(10):3469–3485. doi:10.1039/D2BM01970A
153. Ghaferi M, Raza A, Koohi M, et al. Impact of PEGylated liposomal doxorubicin and carboplatin combination on glioblastoma. *Pharmaceutics*. 2022;14(10):2183. doi:10.3390/pharmaceutics14102183
154. Zhu L, Liu J, Qiu M, et al. Bacteria-mediated metformin-loaded peptide hydrogel reprograms the tumor immune microenvironment in glioblastoma. *Biomaterials*. 2022;288:121711. doi:10.1016/j.biomaterials.2022.121711
155. Wang B, Li H, Yao Q, et al. Local in vitro delivery of rapamycin from electrospun PEO/PDLLA nanofibers for glioblastoma treatment. *Biomed Pharmacother*. 2016;83:1345–1352. doi:10.1016/j.biopha.2016.08.033
156. Steffens L, Morás AM, Arantes PR, et al. Electrospun PVA-Dacarbazine nanofibers as a novel nano brain-implant for treatment of glioblastoma: in silico and in vitro characterization. *Eur J Pharm Sci*. 2020;143:105183. doi:10.1016/j.ejps.2019.105183
157. Tan AC, Ashley DM, López GY, Malinzak M, Friedman HS, Khasraw M. Management of glioblastoma: state of the art and future directions. *CA Cancer J Clin*. 2020;70(4):299–312. doi:10.3322/caac.21613
158. Brown CE, Rodriguez A, Palmer J, et al. Off-the-shelf, steroid-resistant, IL13Rα2-specific CAR T cells for treatment of glioblastoma. *Neuro Oncol*. 2022;24(8):1318–1330. doi:10.1093/neuonc/noac024
159. Wang K, Jiang J, Li P, et al. Electrospinning and electrospun polysaccharide-based nanofiber membranes: a review. *Int J Biol Macromol*. 2024;263(Pt 2):130335. doi:10.1016/j.ijbiomac.2024.130335
160. Wang H, Jiao D, Feng D, et al. Transformable supramolecular self-assembled peptides for cascade self-enhanced ferroptosis primed cancer immunotherapy. *Adv Mater*. 2024;36(21):e2311733. doi:10.1002/adma.202311733
161. Shetty K, Yadav KS. Temozolomide nano-in-nanofiber delivery system with sustained release and enhanced cellular uptake by U87MG cells. *Drug Dev Ind Pharm*. 2024;50(5):420–431. doi:10.1080/03639045.2024.2332906
162. Yang Y, Zhang R, Liang Z, et al. Application of electrospun drug-loaded nanofibers in cancer therapy. *Polymers*. 2024;16(4):1.
163. Li H, Gong Q, Luo K. Biomarker-driven molecular imaging probes in radiotherapy. *Theranostics*. 2024;14(10):4127–4146. doi:10.7150/thno.97768
164. Manem VS, Taghizadeh-Hesary F. Advances in personalized radiotherapy. *BMC Cancer*. 2024;24(1):556. doi:10.1186/s12885-024-12317-3
165. Tang M, Lin K, Ramachandran M, et al. A mitochondria-targeting lipid-small molecule hybrid nanoparticle for imaging and therapy in an orthotopic glioma model. *Acta Pharm Sin B*. 2022;12(6):2672–2682. doi:10.1016/j.apsb.2022.04.005
166. Chen Q, Wang C, Zhang X, et al. In situ sprayed bioresponsive immunotherapeutic gel for post-surgical cancer treatment. *Nat Nanotechnol*. 2019;14(1):89–97. doi:10.1038/s41565-018-0319-4

167. Li W, Zhang G, Liu L. Near-infrared inorganic nanomaterials for precise diagnosis and therapy. *Front Bioeng Biotechnol*. 2021;9:768927. doi:10.3389/fbioe.2021.768927
168. Yu Y, Wang A, Wang S, et al. Efficacy of temozolomide-conjugated gold nanoparticle photothermal therapy of drug-resistant glioblastoma and its mechanism study. *mol Pharm*. 2022;19(4):1219–1229. doi:10.1021/acs.molpharmaceut.2c00083
169. Zhang Z, Feng J, Zhang T, Gao A, Sun C. Application of tumor pH/hypoxia-responsive nanoparticles for combined photodynamic therapy and hypoxia-activated chemotherapy. *Front Bioeng Biotechnol*. 2023;11:1197404. doi:10.3389/fbioe.2023.1197404
170. Guo X, Han L, Chen W, et al. Hypoxia and singlet oxygen dual-responsive micelles for photodynamic and chemotherapy therapy featured with enhanced cellular uptake and triggered cargo delivery. *Int J Nanomedicine*. 2024;19:247–261. doi:10.2147/IJN.S432407
171. Fourniols T, Randolph LD, Staub A, et al. Temozolomide-loaded photopolymerizable PEG-DMA-based hydrogel for the treatment of glioblastoma. *J Control Release*. 2015;210:95–104. doi:10.1016/j.jconrel.2015.05.272
172. Huang X, Chen T, Mu N, et al. Supramolecular micelles as multifunctional theranostic agents for synergistic photodynamic therapy and hypoxia-activated chemotherapy. *Acta Biomater*. 2021;131:483–492. doi:10.1016/j.actbio.2021.07.014
173. Morello A, Bianconi A, Rizzo F, et al. Laser interstitial thermotherapy (LITT) in recurrent glioblastoma: what window of opportunity for this treatment? *Technol Cancer Res Treat*. 2024;23:15330338241249026. doi:10.1177/15330338241249026
174. Jiang H, Wang C, Guo Z, Wang Z, Liu L. Silver nanocrystals mediated combination therapy of radiation with magnetic hyperthermia on glioma cells. *J Nanosci Nanotechnol*. 2012;12(11):8276–8281. doi:10.1166/jnn.2012.6626
175. Beola L, Iturrioz-Rodríguez N, Pucci C, Bertorelli R, Ciofani G. Drug-loaded lipid magnetic nanoparticles for combined local hyperthermia and chemotherapy against glioblastoma multiforme. *ACS Nano*. 2023;17(18):18441–18455. doi:10.1021/acsnano.3c06085
176. Yin M, Yuan Y, Huang Y, et al. Carbon-iodine polydiacetylene nanofibers for image-guided radiotherapy and tumor-microenvironment-enhanced radiosensitization. *ACS Nano*. 2024;18(11):8325–8336. doi:10.1021/acsnano.3c12623
177. Zhang S, Jiao X, Heger M, et al. A tumor microenvironment-responsive micelle co-delivered radiosensitizer Dbait and doxorubicin for the collaborative chemo-radiotherapy of glioblastoma. *Drug Deliv*. 2022;29(1):2658–2670. doi:10.1080/10717544.2022.2108937
178. Luo H, Cao H, Jia H, et al. EISA in tandem with ICD to form in situ nanofiber vaccine for enhanced tumor radioimmunotherapy. *Adv Healthc Mater*. 2023;12(27):e2301083. doi:10.1002/adhm.202301083
179. Nienhaus K, Nienhaus GU. Mechanistic understanding of protein corona formation around nanoparticles: old puzzles and new insights. *Small*. 2023;19(28):e2301663. doi:10.1002/smll.202301663
180. Bobo D, Robinson KJ, Islam J, Thurecht KJ, Corrie SR. Nanoparticle-based medicines: a review of FDA-approved materials and clinical trials to date. *Pharm Res*. 2016;33(10):2373–2387. doi:10.1007/s11095-016-1958-5
181. Ren J, Andrikopoulos N, Velonia K, et al. Chemical and biophysical signatures of the protein corona in nanomedicine. *J Am Chem Soc*. 2022;144(21):9184–9205. doi:10.1021/jacs.2c02277
182. Tomak A, Cesmeli S, Hanoglu BD, Winkler D, Oksel Karakus C. Nanoparticle-protein Corona complex: understanding multiple interactions between environmental factors, corona formation, and biological activity. *Nanotoxicology*. 2021;15(10):1331–1357. doi:10.1080/17435390.2022.2025467
183. Khan S, Sharifi M, Gleghorn JP, et al. Artificial engineering of the protein Corona at bio-nano interfaces for improved cancer-targeted nanotherapy. *J Control Release*. 2022;348:127–147.
184. Bilardo R, Traldi F, Vdovchenko A, Resmini M. Influence of surface chemistry and morphology of nanoparticles on protein Corona formation. *Wiley Interdiscip Rev Nanomed Nanobiotechnol*. 2022;14(4):e1788.
185. Randhawa S, Abidi SMS, Dar AI, Acharya A. The curious cases of nanoparticle induced amyloidosis during protein Corona formation and anti-amyloidogenic nanomaterials: paradox or prejudice? *Int J Biol Macromol*. 2021;193:1009–1020. doi:10.1016/j.ijbiomac.2021.10.195
186. Hajipour MJ, Safavi-Sohi R, Sharifi S, et al. An Overview of Nanoparticle Protein Corona Literature. *Small*. 2023;19(36):e2301838. doi:10.1002/smll.202301838
187. Rodrigues CF, Fernandes N, de Melo-Diogo D, Correia IJ, Moreira AF. Cell-derived vesicles for nanoparticles' coating: biomimetic approaches for enhanced blood circulation and cancer therapy. *Adv Healthc Mater*. 2022;11(23):e2201214. doi:10.1002/adhm.202201214
188. Ahmadabad LE, Kalantari FS, Liu H, et al. Hydrothermal method-based synthesized tin oxide nanoparticles: albumin binding and antiproliferative activity against K562 cells. *Mater Sci Eng C Mater Biol Appl*. 2021;119:111649. doi:10.1016/j.msec.2020.111649
189. Arsalan N, Hassan Kashi E, Hasan A, et al. Exploring the interaction of cobalt oxide nanoparticles with albumin, leukemia cancer cells and pathogenic bacteria by multispectroscopic, docking, cellular and antibacterial approaches. *Int J Nanomed*. 2020;15:4607–4623. doi:10.2147/IJN.S257711
190. Déciga-Alcaraz A, Medina-Reyes EI, Delgado-Buenrostro NL, et al. Toxicity of engineered nanomaterials with different physicochemical properties and the role of protein Corona on cellular uptake and intrinsic ROS production. *Toxicology*. 2020;442:152545. doi:10.1016/j.tox.2020.152545
191. Asadian M, Dhaenens M, Onyshchenko I, et al. Plasma functionalization of polycaprolactone nanofibers changes protein interactions with cells, resulting in increased cell viability. *ACS Appl Mater Interfaces*. 2018;10(49):41962–41977. doi:10.1021/acsami.8b14995
192. Al-Nakashli R, Raveendran R, Khine YY, et al. Drug-loading content influences cellular uptake of polymer-coated nanocellulose. *mol Pharm*. 2023;20(4):2017–2028. doi:10.1021/acs.molpharmaceut.2c00997
193. Huo T, Yang Y, Qian M, et al. Versatile hollow COF nanospheres via manipulating transferrin Corona for precise glioma-targeted drug delivery. *Biomaterials*. 2020;260:120305. doi:10.1016/j.biomaterials.2020.120305
194. Cai R, Chen C. The crown and the scepter: roles of the protein corona in nanomedicine. *Adv Mater*. 2019;31(45):e1805740. doi:10.1002/adma.201805740
195. Wang YF, Zhou Y, Sun J, et al. The Yin and Yang of the protein Corona on the delivery journey of nanoparticles. *Nano Res*. 2023;16(1):715–734. doi:10.1007/s12274-022-4849-6
196. Thermodynamic and conformational changes of protein toward interaction with nanoparticles: a spectroscopic overview. 2016.
197. Hofer S, Hofstätter N, Punz B, Hasenkopf I, Johnson L, Himly M. Immunotoxicity of nanomaterials in health and disease: current challenges and emerging approaches for identifying immune modifiers in susceptible populations. *Wiley Interdiscip Rev Nanomed Nanobiotechnol*. 2022;14(6):e1804. doi:10.1002/wnan.1804

198. Mueller S, Kline C, Stoller S, et al. PNOC015: repeated convection-enhanced delivery of MTX110 (aqueous panobinostat) in children with newly diagnosed diffuse intrinsic pontine glioma. *Neuro Oncol*. 2023;25(11):2074–2086. doi:10.1093/neuonc/noad105
199. Verry C, Dufort S, Villa J, et al. Theranostic AGuIX nanoparticles as radiosensitizer: a Phase I, dose-escalation study in patients with multiple brain metastases (NANO-RAD trial). *Radiother Oncol*. 2021;160:159–165. doi:10.1016/j.radonc.2021.04.021
200. Bennett S, Verry C, Kaza E, et al. Quantifying gadolinium-based nanoparticle uptake distributions in brain metastases via magnetic resonance imaging. *Sci Rep*. 2024;14(1):11959. doi:10.1038/s41598-024-62389-1
201. Kumthekar P, Ko CH, Paunesku T, et al. A first-in-human phase 0 clinical study of RNA interference-based spherical nucleic acids in patients with recurrent glioblastoma. *Sci Transl Med*. 2021;13(584). doi:10.1126/scitranslmed.abb3945.
202. Elinzano H, Toms S, Robison J, et al. Nanoliposomal irinotecan and metronomic temozolomide for patients with recurrent glioblastoma: bruog329, a phase i brown university oncology research group trial. *Am J Clin Oncol*. 2021;44(2):49–52. doi:10.1097/COC.0000000000000780
203. Neamtu B, Barbu A, Negrea MO, et al. Carrageenan-based compounds as wound healing materials. *Int J Mol Sci*. 2022;23(16). doi:10.3390/ijms23169117
204. Campiglio CE, Contessi Negrini N, Farè S, Draghi L. Cross-linking strategies for electrospun gelatin scaffolds. *Materials*. 2019;12(15). doi:10.3390/ma12152476
205. Madamsetty VS, Mohammadinejad R, Uzieliene I, et al. Dexamethasone: insights into pharmacological aspects, therapeutic mechanisms, and delivery systems. *ACS Biomater Sci Eng*. 2022;8(5):1763–1790. doi:10.1021/acsbiomaterials.2c00026
206. Shikhi-Abadi PG, Irani M. A review on the applications of electrospun chitosan nanofibers for the cancer treatment. *Int J Biol Macromol*. 2021;183:790–810. doi:10.1016/j.ijbiomac.2021.05.009
207. Ristic B, Harhaji-Trajkovic L, Bosnjak M, Dakic I, Mijatovic S, Trajkovic V. Modulation of cancer cell autophagic responses by graphene-based nanomaterials: molecular mechanisms and therapeutic implications. *Cancers*. 2021;13(16):1.
208. Real DA, Bolaños K, Priotti J, et al. Cyclodextrin-modified nanomaterials for drug delivery: classification and advances in controlled release and bioavailability. *Pharmaceutics*. 2021;13(12):2131. doi:10.3390/pharmaceutics13122131
209. Meylina L, Muchtaridi M, Joni IM, Mohammed AFA, Wathoni N. Nanoformulations of α-mangostin for cancer drug delivery system. *Pharmaceutics*. 2021;13(12):1993. doi:10.3390/pharmaceutics13121993
210. Mbituyimana B, Liu L, Ye W, et al. Bacterial cellulose-based composites for biomedical and cosmetic applications: research progress and existing products. *Carbohydr Polym*. 2021;273:118565. doi:10.1016/j.carbpol.2021.118565
211. Narmani A, Rezvani M, Farhood B, et al. Folic acid functionalized nanoparticles as pharmaceutical carriers in drug delivery systems. *Drug Dev Res*. 2019;80(4):404–424. doi:10.1002/ddr.21545
212. Ma A, Ran H, Wang J, et al. An urchin-shaped copper-based metalloporphyrin nanosystem as a sonosensitizer for sonodynamic therapy. *Nanomaterials*. 2022;12(2):209. doi:10.3390/nano12020209
213. Du J, Sun J, Liu X, et al. Preparation of C6 cell membrane-coated doxorubicin conjugated manganese dioxide nanoparticles and its targeted therapy application in glioma. *Eur J Pharm Sci*. 2023;180:106338. doi:10.1016/j.ejps.2022.106338
214. Yin C, Li Y, Liao Z, et al. Live bio-nano-sonosensitizer targets malignant tumors in synergistic therapy. *Acta Biomater*. 2023;155:491–506. doi:10.1016/j.actbio.2022.11.037
215. Zhang B, Xue R, Sun C. Rational design of ROS-responsive nanocarriers for targeted X-ray-induced photodynamic therapy and cascaded chemotherapy of intracranial glioblastoma. *Nanoscale*. 2022;14(13):5054–5067. doi:10.1039/d2nr00436d
216. Mohammadi MA, Alizadeh AM, Mousavi M, et al. Advances and applications of crosslinked electrospun biomacromolecular nanofibers. *Int J Biol Macromol*. 2024;271(Pt 2):132743. doi:10.1016/j.ijbiomac.2024.132743
217. Aragon-Sanabria V, Aditya A, Zhang L, et al. Ultrasmall nanoparticle delivery of doxorubicin improves therapeutic index for high-grade glioma. *Clin Cancer Res*. 2022;28(13):2938–2952. doi:10.1158/1078-0432.CCR-21-4053
218. Gao M, Chen Y, Wu C. Size-dependent chemosensitization of doxorubicin-loaded polymeric nanoparticles for malignant glioma chemotherapy. *Bioengineered*. 2021;12(2):12263–12273. doi:10.1080/21655979.2021.2006568
219. Wang HB, Mullins ME, Cregg JM, McCarthy CW, Gilbert RJ. Varying the diameter of aligned electrospun fibers alters neurite outgrowth and Schwann cell migration. *Acta Biomater*. 2010;6(8):2970–2978. doi:10.1016/j.actbio.2010.02.020
220. Valizadeh A, Asghari S, Abbaspoor S, Jafari A, Raeisi M, Pilehvar Y. Implantable smart hyperthermia nanofibers for cancer therapy: challenges and opportunities. *Wiley Interdisciplinary Rev Nanomed Nanobiotechnol*. 2023;15(6):e1909. doi:10.1002/wnan.1909
221. Lin X, Long H, Zhong Z, Ye Q, Duan B. Biodegradable chitin nanofiber-alginate dialdehyde hydrogel: an injectable, self-healing scaffold for anti-tumor drug delivery. *Int J Biol Macromol*. 2024;270(Pt 2):132187. doi:10.1016/j.ijbiomac.2024.132187
222. Hong J, Wu D, Wang H, et al. Magnetic fibrin nanofiber hydrogel delivering iron oxide magnetic nanoparticles promotes peripheral nerve regeneration. *Regen Biomater*. 2024;11:rbae075. doi:10.1093/rb/rbae075
223. Liu X, Ren Y, Fu S, et al. Toward morphologically relevant extracellular matrix: nanofiber-hydrogel composites for tumor cell culture. *J Mater Chem B*. 2024;12(16):3984–3995. doi:10.1039/d3tb02575f
224. Zhang L, Teng F, Xin H, et al. A big prospect for hydrogel nano-system in glioma. *Int J Nanomedicine*. 2024;19:5605–5618. doi:10.2147/IJN.S470315
225. Turabee MH, Jeong TH, Ramalingam P, Kang JH, Ko YT. N,N,N-trimethyl chitosan embedded in situ Pluronic F127 hydrogel for the treatment of brain tumor. *Carbohydr Polym*. 2019;203:302–309. doi:10.1016/j.carbpol.2018.09.065
226. Stupp R, Taillibert S, Kanner A, et al. Effect of tumor-treating fields plus maintenance temozolomide vs maintenance temozolomide alone on survival in patients with glioblastoma: a randomized clinical trial. *JAMA*. 2017;318(23):2306–2316. doi:10.1001/jama.2017.18718
227. Gao X, Qian J, Zheng S, et al. Overcoming the blood-brain barrier for delivering drugs into the brain by using adenosine receptor nanoagonist. *ACS Nano*. 2014;8(4):3678–3689. doi:10.1021/nn5003375