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Review Article

# Recent advances in spatio-temporally controllable systems for management of glioma

*Huiwen Zhang*[a,1], *Wanqi Zhu*[a,1], *Wei Pan*[a], *Xiuyan Wan*[a,*], *Na Li*[a,*], *Bo Tang*[a,b,*]

[a] *College of Chemistry, Chemical Engineering and Materials Science, Key Laboratory of Molecular and Nano Probes, Ministry of Education, Collaborative Innovation Center of Functionalized Probes for Chemical Imaging in Universities of Shandong, Institute of Molecular and Nano Science, Shandong Normal University, Jinan 250014, China*

[b] *Laoshan Laboratory, Qingdao 266237, China*

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ABSTRACT

Malignant glioma remains one of the most aggressive intracranial tumors with devastating clinical outcomes despite the great advances in conventional treatment approaches, including surgery and chemotherapy. Spatio-temporally controllable approaches to glioma are now being actively investigated due to the preponderance, including spatio-temporal adjustability, minimally invasive, repetitive properties, etc. External stimuli can be readily controlled by adjusting the site and density of stimuli to exert the cytotoxic on glioma tissue and avoid undesired injury to normal tissues. It is worth noting that the removability of external stimuli allows for on-demand treatment, which effectively reduces the occurrence of side effects. In this review, we highlight recent advancements in drug delivery systems for spatio-temporally controllable treatments of glioma, focusing on the mechanisms and design principles of sensitizers utilized in these controllable therapies. Moreover, the potential challenges regarding spatio-temporally controllable therapy for glioma are also described, aiming to provide insights into future advancements in this field and their potential clinical applications.



## 1. Introduction

Gliomas, including astrocytomas (such as astrocytoma, anaplastic astrocytoma, and glioblastoma multiforme), oligodendrogliomas and mixed gliomas, represent a group of highly aggressive primary brain tumors in adults, characterized by limited overall survival [1,2]. The origin of glioma cells is not fully understood and may arise from various precursor cells, including neural stem cells, glial progenitors, or mature cells that undergo dedifferentiation. These cells can give rise to tumors of mixed lineages, such as glioneuronal tumors [3]. The 2021 classification of central nervous system tumors by WHO divides adult

* Corresponding authors.
*E-mail addresses:* wanxy@sdnu.edu.cn (X. Wan), lina@sdnu.edu.cn (N. Li), tangb@sdnu.edu.cn (B. Tang).
[1] These authors contributed equally to this work
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diffuse gliomas into three types: astrocytoma with isocitrate dehydrogenase (IDH) mutation, oligodendroglioma with IDH mutation and 1p/19q codeletion, and glioblastoma (GBM) with IDH wild-type. Each type of tumor is further divided into grades, with astrocytoma IDH mutant graded as CNS WHO 2–4 and oligodendroglioma with IDH mutation and 1p/19q codeletion graded as CNS WHO 2–3. Despite their classification and pathology, all gliomas are characterized by a unique microenvironment, including oxidative stress, hypoxia, and angiogenesis. Also, their treatments are hindered by the presence of the blood-brain barrier (BBB) and blood-brain tumor barrier (BBTB) [4].

Currently, operative treatment followed by adjuvant chemotherapy is the standard strategy for the management of glioma and has remained largely unchanged for the last few decades [5]. But it is nearly impossible to distinguish the margins of gliomas from normal tissue during surgery due to their rapid infiltration and growth [6]. Hence, surgery cannot eradicate glioma, and only local infiltrative tumor foci can be removed to avoid causing neurological deficits in patients [1]. During chemotherapy process, patients frequently and rapidly develop acquired drug resistance, which ultimately leads to disappointing outcomes [7]. Uncontrolled drug release may also cause serious systemic toxicity with limited therapeutic efficacy [8,9]. Further, the existence of BBB and BBTB, which also prevents most drug candidates from reaching glioma cells, greatly reduces the efficiency of chemotherapy [10-12]. The current countermeasure of inefficient chemotherapy is increasing drug doses, which generally cause intolerable side effects, resulting in more severe systemic toxicity. Besides chemotherapy, radiotherapy (RT) is another adjuvant treatment modality for malignant gliomas in the clinic [13]. Although it can effectively induce apoptosis and necrosis of glioma cells, several factors may constrain the efficacy of RT, including the hypoxic tumor microenvironment (TME), the low radiation absorption and the varied regulatory signaling pathways of glioma [14,15]. Merely irradiating glioma tissue is insufficient to achieve the desired therapeutic outcome. Therefore, from a long-term perspective, patients with glioma urgently require strategies that can overcome these barriers with minimal side effects. Ongoing basic research into glioma treatment, along with expanding understanding of glioma pathology, provides a firm foundation for development of novel and more effective strategies, as well as for improvement of existing approaches, to achieve superior glioma therapy.

To date, the application of external controllable stimuli, including laser, ultrasound (US), radiation, and magnet, as remote controls for glioma treatment has attracted considerable attention. Compared with conventional therapy of glioma, the spatio-temporally controllable approaches have many unique features: (1) External controllable stimuli can be precisely targeted to specific locations of the brain where the glioma is located for targeted glioma therapy [4,16]. (2) By having the ability to remove external stimuli, on-demand treatment becomes feasible, resulting in a significant reduction in side effects. This approach emphasizes a safer and more efficient way of treating glioma. (3) The non-invasive character of external controllable stimuli significantly reduces the risks associated with surgical procedures, minimizing damage to surrounding normal tissue [13,17]. (4) The spatio-temporally controllable systems can be readily customized by adjusting the spatial targeting, intensity, duration, and frequency of external stimuli for tailored glioma therapy. (5) It is very convenient to combine external controllable stimuli-based therapy with other treatments such as chemotherapy, chemodynamic therapy (CDT), and immunotherapy, offering great potential to improve the efficacy of glioma treatment [18,19].

The rational design and utilization of sensitizers provide firm foundations for advanced spatio-temporally controllable treatments. Currently, numerous new molecules and materials that generate harmful species in response to specific stimuli have been introduced into spatio-temporally controllable systems. These materials include, but are not limited to, organic molecules, inorganic materials, liposomes, micelles, and composite materials [20-23]. Notably, nanoparticles have been effectively designed to treat glioma by incorporating multiple sensitizers through adsorption, covalent linkage, or encapsulation for spatio-temporally controllable therapy. Chemical modification and conjugation techniques enable the attachment of specific ligands to nanoparticles, enhancing their ability to target glioma tissues through BBB penetration due to their large specific surface area [10]. In addition, some of the organic sensitizers, such as 5-aminolevulinic acid (5-ALA), hematoporphyrin, and chlorine e6 (Ce6), serve not only as photodynamic therapy (PDT) sensitizers but also afford sonodynamic therapy (SDT) for glioma treatment [24-26]. Gold nanoparticles, meanwhile, possess both radiosensitizing effects and the capability to conduct photothermal therapy (PTT). Based on the rational concordant collaboration of various advanced materials within spatio-temporally controllable systems, these specific treatment strategies represent attractive tools for efficient glioma therapy. In this review, we focus primarily on glioma therapies that utilize various external controllable stimuli (Fig. 1), discussing their advantages and recent advancements in recent years, especially in terms of their primary mechanisms and the selection of sensitizers. Finally, the challenges for clinical translation of glioma therapies based on external controllable stimuli are discussed.

## 2. Photo-based spatio-temporally controllable glioma therapy

Over the past few decades, significant attention has been devoted to the distinct features and tremendous progress in phototherapy, including PDT and PTT, in the management of glioma [27-29]. The non-invasive and highly controllable nature of phototherapy has made it a universal approach for effective glioma treatment with minimal side effects [30,31]. Localized irradiation with externally controlled light at the lesion sites is considered to be effective, especially following aggressive tumor resection. Various controllable factors, including power, light scattering, light density and irradiation site, are modulated to achieve greater therapeutic efficiency. PDT and PTT trigger reactive oxygen species (ROS) and regional hyperthermia, respectively, giving rise to irreparable apoptotic and necrotic death of glioma cells

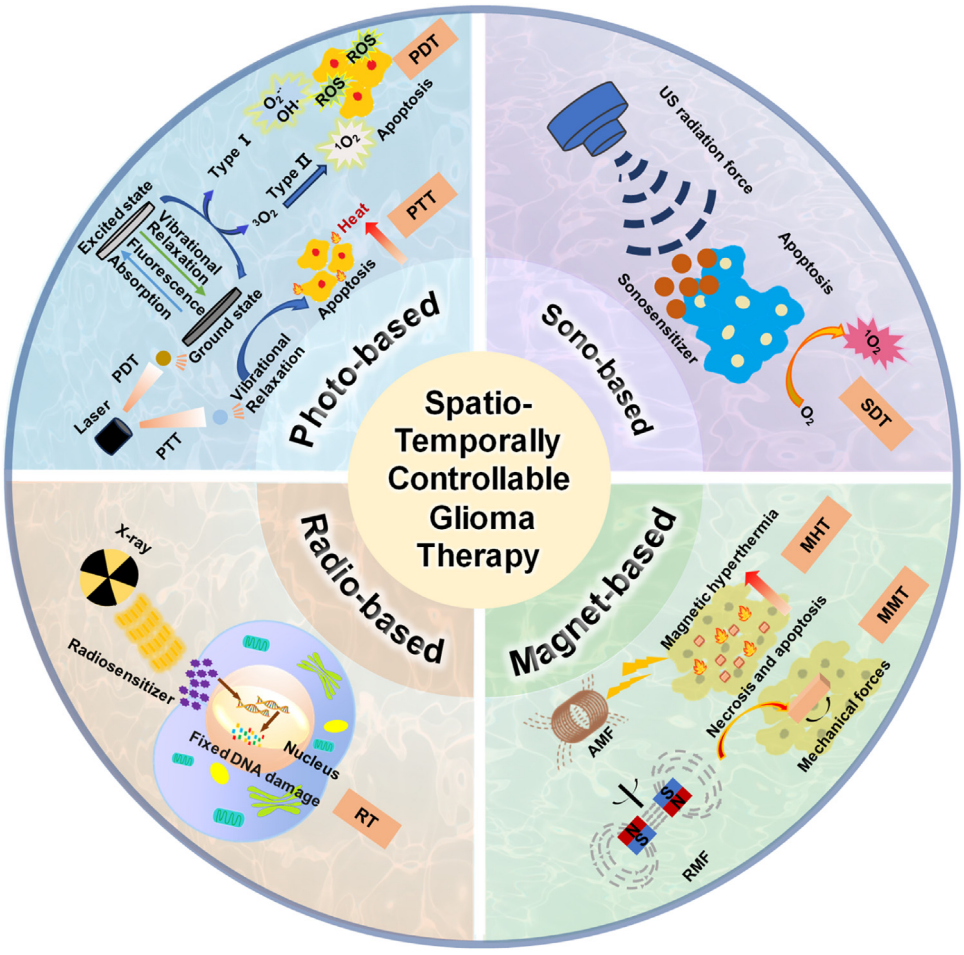


**Fig. 1 – A schematic overview of the spatio-temporally controllable glioma therapy.**

[32]. Hence, PDT and PTT are widely exploited to treat glioma tissues with enhanced selectivity and controllability, demonstrating tremendous potential for improving the accuracy and effectiveness of glioma therapy.

## 2.1. PDT

In 1900, Oscar Raab, a German medical student, discovered that the combination of chemicals and light could cause cell death. This finding led to the development of PDT, which relies on three significant ingredients for its function: a photosensitizer (PS), light, and molecular oxygen [33-35]. The PS, once localized in the brain, is irradiated with a spatio-temporally controllable laser. It absorbs light at a specific wavelength and performs photochemical reactions, converting oxygen into ROS, which makes PS the most important factor in the process. This reaction process, involving the excitation and transition of molecules from a ground state to an excited singlet state via the absorption of energy, is fundamental to the therapy [36]. *In vivo*, the produced ROS induces oxidative stress, leading to glioma cell necrosis, apoptosis, and even tumor microvascular injury [37]. The upcoming sections will detail various well-designed PDT systems for glioma according to therapy elements.

### 2.1.1. *Types and delivery of PSs*

Given the limited efficiency of the generation of ROS, particularly singlet oxygen, the selection of PSs can be pivotal for therapeutic impact. PDT for glioma has employed a variety of PSs, including derivatives of 5-ALA, Ce6, methylene blue (MB), and talaporfin sodium [38-44]. Phthalocyanine and its derivatives, which can achieve deep tissue penetration, are also commonly used as PSs in PDT for glioma; nevertheless, the hydrophobic properties of these PSs greatly limit their application, as it leads to aggregation in solution. Thus, a series of methods to change the solubility of phthalocyanine derivatives have been developed, with the aim of achieving more efficient treatment for glioma [45-48]. For instance, Gan et al. reported the anti-glioma effect of water-soluble zinc phthalocyanine tetrasulfonate combined with bovine serum albumin [45]. Broome's group has successfully utilized Au nanoparticles with different ligands to load the PS phthalocyanine 4. This approach protected the optical properties of the PS and improved its targeting, thus demonstrating a successful design for glioma therapy [47,48]. Moreover, inorganic materials have been used as PSs to efficiently generate ROS for glioma ablation. Yang et al. have developed black phosphorus quantum dots (BP QDs) coordinated with $Nd^{3+}$ ions. The BP QDs exhibited exceptional

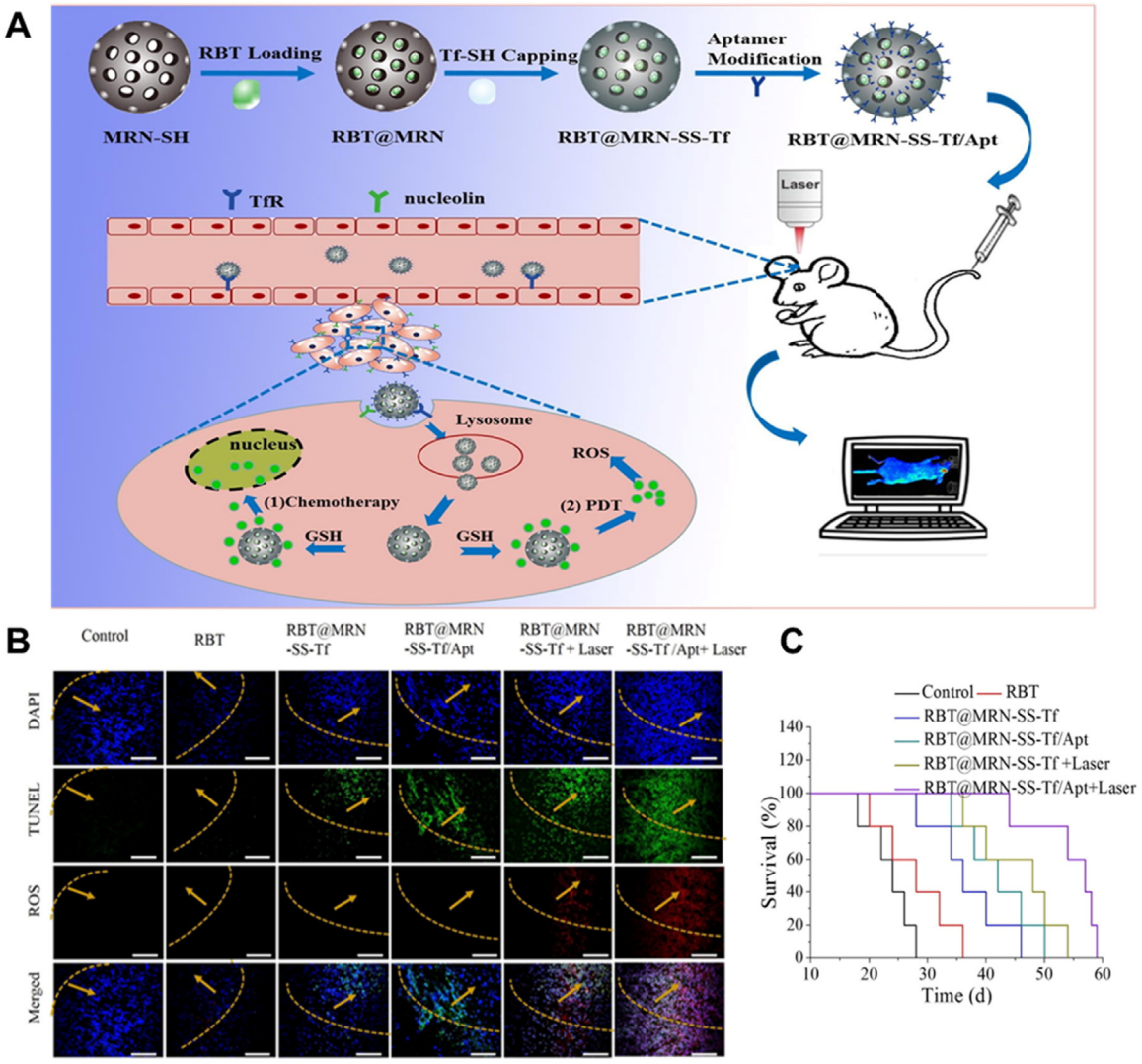


**Fig. 2 – (A) Schematic illustration of RBT@MRN-SS-Tf/Apt nanoparticles for combinatory glioma therapy; (B) Tumor apoptosis of mice bearing glioma after intravenous injection of saline, RBT, RBT@MRN-SS-Tf or RBT@MRN-SS-Tf/Apt; (C) Survival curves of glioma-bearing mice in different groups ($n$ = 5). Scale bars: 50 μm. Reproduced with permission from [53], Copyright 2018 Elsevier Ltd.**

photochemical properties and could also carry drugs; their ultrasmall size made them capable of crossing the BBB. The team analyzed the quantum dots for intracranial fluorescence imaging and X-ray-generated photodynamic performance [49]. The $^1O_2$ produced by the transfer of X-ray photon energy from the $Nd^{3+}$ ions in BP QDs significantly suppressed GBM growth. Additionally, other novel PSs, such as aggregation-induced emission (AIE) PS and nano-aggregates, have been utilized to promote the production of ROS [50,51]. An up-conversion nanoparticle (UCNP; $NaGdF_4$:Yb, Tm@$NaYF_4$:Yb, and Nd@$NaYF_4$) formed the core of a multifunctional nanoparticle with a PS metal-organic framework (MOF) shell, enabling deep therapy of glioma though the conversion of 808 nm light to ultraviolet light, excited by $Nd^{3+}$ doping, which in turn induces near-infrared (NIR)-mediated PDT of glioma [22].

Selective activation and targeted delivery of PSs is an interesting field in PDT of glioma. Sun and colleagues have developed a new type of small molecule probe that switch “on” and “off”. The probe contained a PS called MB, which can only be activated by the overexpression of HDAC6 in GBM tissue. Upon activation, MB was released, helping to inhibit glioma invasion and induce cell apoptosis. This enhanced the control of PDT and reduced the risk of nonspecific photodamage, thereby making it a promising tool for cancer treatment [52]. Liu et al. used glioma-targeting transferrin and aptamer AS1411 as capping agents for an engineered nanomaterial, which allowed for the controlled release of PSs within the body (Fig. 2A) [53]. In the presence of laser irradiation, controllable PDT was performed through the cleavage of disulfide bonds facilitated by endogenous GSH within glioma cells as the nanosystem traversed the BBB to reach glioma lesions. As

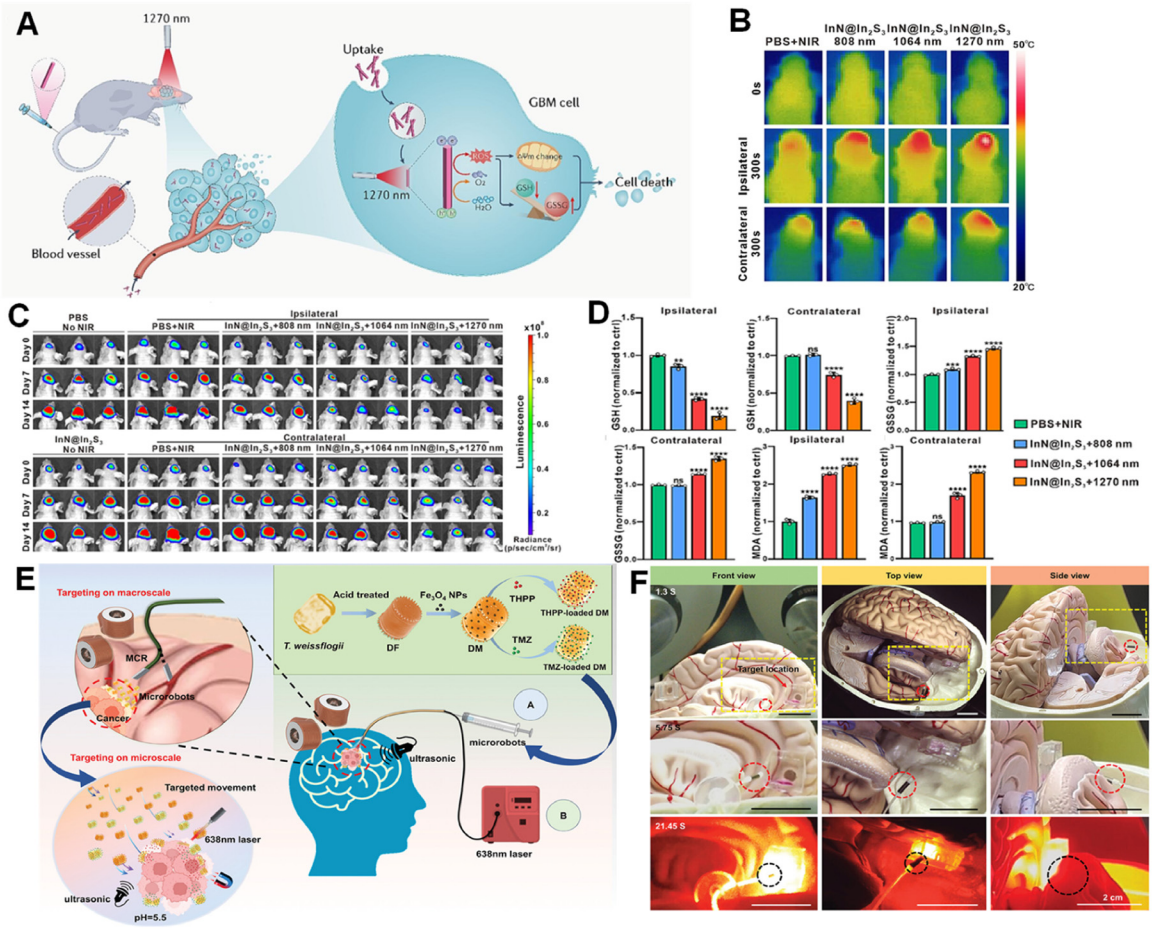


**Fig. 3 – (A) Schematic illustration of InN@$In_2S_3$ producing $O_2$ and ROS under 1270 nm laser irradiation. (B) Infrared thermal images of mice treated with PBS or InN@In2S3 (40 mg $kg^{-1}$) under different laser irradiation. (C) Bioluminescent images of glioma-bearing mice in different groups ($n = 6$). (D) Variations in glutathione (GSH), oxidized glutathione (GSSG), and malondialdehyde (MDA) levels of tumors treated with PBS or InN@In2S3 with different laser irradiation (0.5 W/$cm^2$, 5 min) ipsilaterally and contralaterally. *P < 0.5, **P < 0.1, ***P < 0. 01, ****P < 0.0001. Reproduced with permission from [55], Copyright 2023 Elsevier B.V. (E) Schematic illustration of cross-scale drug delivery based on MCR for combination therapy. (F) Front view, top view, and side view of MCR achieving macroscale delivery of DMs and optical fibers in a brain model. The circles indicate the locations where the MCR arrived. The yellow boxes highlight the expanded area. Reproduced with permission from [18], Copyright 2024 Wiley-VCH GmbH.**

illustrated in Fig. 2B and 2C, this approach increased the accumulation of ROS at the glioma site and potentiated apoptosis in glioma cells, extending the median survival time of glioma-bearing mice.

### 2.1.2. *Light*

The utilization of laser irradiation to activate PSs in glioma tissue is a crucial factor for PDT of glioma. The penetration of light into tissue is a multifaceted process, influenced by the optical properties of the tissue under the specific wavelength of light employed and certain molecular within the tissue that affect light scattering and absorption [33]. Initially, light administration was superficial, illuminating the edges of the excision cavity or directly onto the surface of tumor tissue using laser sources or conventional lamps. Later studies have shifted towards cavity light irradiation or interstitial PDT to achieve deeper tissue penetration, which involves the insertion of single or multiple optical fibers into the excision cavity [54]. Typically, within the commonly used wavelength range of 630–690 nm, light penetration depths in various tissue types range from 1 to 5 mm [43]. To achieve maximum penetration depth in glioma tissue, it is generally necessary to increase the wavelength of the laser. Guo and co-workers reported a heterojunction semiconductor nanomaterial with high electron-hole separation efficiency, which has superior absorption in the NIR regions II (1000–1700 nm), enabling deeper laser penetration (Fig. 3A) [55]. They explored three distinct laser wavelengths (808 nm, 1064 nm and 1270 nm) to assess the effectiveness of ipsilateral and contralateral irradiation in BALB/c mice bearing U87MG-luc tumors. The temperature in the glioma region of the mice increased with the laser wavelength, and ipsilateral irradiation demonstrated superior photothermal efficacy compared to contralateral irradiation (Fig. 3B). *In vivo* studies demonstrated that laser irradiation at 1270 nm induced greater intratumoral oxidative damage in mice compared with lower wavelengths, thereby

demonstrating superior inhibitory effect on glioma growth (Fig. 3C and 3D).

#### 2.1.3. *Oxygen*

Oxygen plays a significant role in PDT, as PSs require oxygen molecules to initiate effective light-induced reactions. However, the lack of oxygen supply in the hypoxic TME can limit the effectiveness of PDT by reducing ROS production. Therefore, it is essential to develop versatile materials that can perform PDT and overcome the hypoxia issue in glioma [56]. Addressing this, Lu et al. constructed mesoporous silicon wrapped with Prussian blue nanoparticles that convert hydrogen peroxide ($H_2O_2$) into oxygen, loaded with 5-ALA for PDT. The therapeutic effect was greatly enhanced, generating augmented cytotoxicity and tumor growth retardation on irradiation [57]. Yang's group employed the catalase hemin to produce oxygen *in situ*, assisting the PS zinc-phthalocyanine in overcoming hypoxic conditions for superior PDT efficacy [58]. In addition, a redox reaction of manganese oxide ($MnO_2$) and $H_2O_2$ from glucose oxidase (GOx) was applied to generate oxygen to improve the curative effect of PDT in an acidic TME. The synergistic effect of PDT with indocyanine green (ICG) and starvation therapy using GOx, with the help of lactoferrin, resulted in BBB penetration and glioma targeting capacities, significantly inhibiting glioma growth [59].

#### 2.1.4. *PDT-derived multimodal synergistic therapy*

It has been reported that tumor cells resistance to chemotherapy often involves the efflux of drugs by P-glycoprotein. PDT has been demonstrated to have the potential to inhibit the expression of P-glycoprotein across several human tumor cell lines. Thus, combining PDT with chemotherapy drugs like temozolomide (TMZ), doxorubicin (DOX), lapatinib, and dihydroartemisinin has demonstrated effective in glioma-bearing models, highlighting their potential clinical value for glioma therapy [60-63]. Luo et al. created a nanogel crosslinked with pullulan and ROS-degradable conjugated poly (deca-4,6-diynedioic acid), loaded with PS ICG, and the chemotherapeutic drug TMZ for controlled drug release. With precise spatio-temporally controllable NIR irradiation, the nanogel could traverse the BBB and accumulate deeply in GBM lesions, potentially enhancing brain tumor treatment [23]. Furthermore, Jiao et al. fabricated a novel magnetic continuum robot (MCR) to deliver optical fibers for PDT and two different microrobots loaded with TMZ and PS 5,10,15,20-tetrakis(4-hydroxyphenyl) porphyrin (THPP) for the combined chemotherapy and PDT of deep-seated GBM to circumvent the constraints associated with light penetration (Fig. 3E). The microrobots, covered with a large number of magnetic particles, exhibited excellent superparamagnetic properties, thereby enabling controlled motion under a magnetic field. The PS THPP loaded into the cavity of microrobots could be released explosively, facilitated by the microrobots' susceptibility to disruption under US. As shown in Fig. 3F, the authors demonstrated the capability of MCR to transmit optical fibers and microrobots at the macroscale in brain model, achieving targeted spatial aggregation and timely release for spatio-temporally controllable PDT therapy of GBM [18].

### 2.2. *PTT*

Photothermal agents (PTAs) harness laser irradiation to convert light energy into localized heat through electron excitation and non-radiative relaxation processes [64-66]. This rise in intracellular interstitial temperature significantly affects the bioactivity of multiple enzymes and structural proteins, the synthesis of nucleic acids, and the conformation of DNA. Further, photothermal media accumulating in glioma tissue induces apoptosis and necrosis of glioma cells after penetrating the BBB with spatio-temporally controllable irradiation, thereby avoiding the unnecessary disruption of non-targeted normal tissue [7]. Next, spatio-temporally controllable systems of PTT were generalized through treatment mechanisms.

#### 2.2.1. *Types and delivery of PTAs*

PTAs are categorized into two groups: organic agents and inorganic agents [13,67-69]. These categories differ in biocompatibility, biodegradability, and photothermal properties. Organic PTAs include small molecules and semiconductor polymers, whereas inorganic PTAs encompass carbon-based nanomaterials, noble metal materials, transition metal materials, etc. Among them, gold nanoparticles are preferred for deep PTT of glioma due to their outstanding physicochemical properties and ultrasmall size [70-72]. In addition, nanoparticles smaller than 12 nm are reported to be able to penetrate the BBB and aggregate in brain tumors. Huang et al. synthesized an 8 nm carbon nanocore with high water dispersion and biocompatibility through *in situ* solid-form synthesis, which demonstrated tunable fluorescence emission and powerful photoacoustic/photothermal performance, enabling efficient thermal ablation of deep-seated glioma tissues under laser irradiation [73].

Effective delivery of PTAs to targeted regions within the glioma tumor area is also a crucial aspect of spatio-temporally controllable PTT. Innovative methods such as cloaking PTAs with immune or homotypic cell membranes have emerged as effective strategies [74,75]. Dai et al. employed GBM patient-derived cell membrane-camouflaged gold nanorods for thermal ablation in orthotopic xenograft mice. Depending on their superior homology, the resulting photothermal reagent exhibited selective targeting to GBM lesions by BBB crossing, avoiding damage to normal tissue [21]. Additionally, Kim's group utilized exosomes derived from U87 cells coated on PTAs Prussian blue nanoparticles to achieve specific targeting and treatment of GBM tumors [68]. Under laser irradiation with controlled position and power density, precise localization of the PTA provided the foundation for spatio-temporally controllable PTT.

#### 2.2.2. *Light*

To overcome challenges like light scattering, absorption, and autofluorescence, new materials emitting light in the NIR range have been developed for glioma phototherapy in recent years [76-78]. ICG, a Food and Drug Administration (FDA)-approved fluorescence dye for medical research, is often used as a photothermal reagent due to its ability to convert absorbed light into hyperthermia effectively

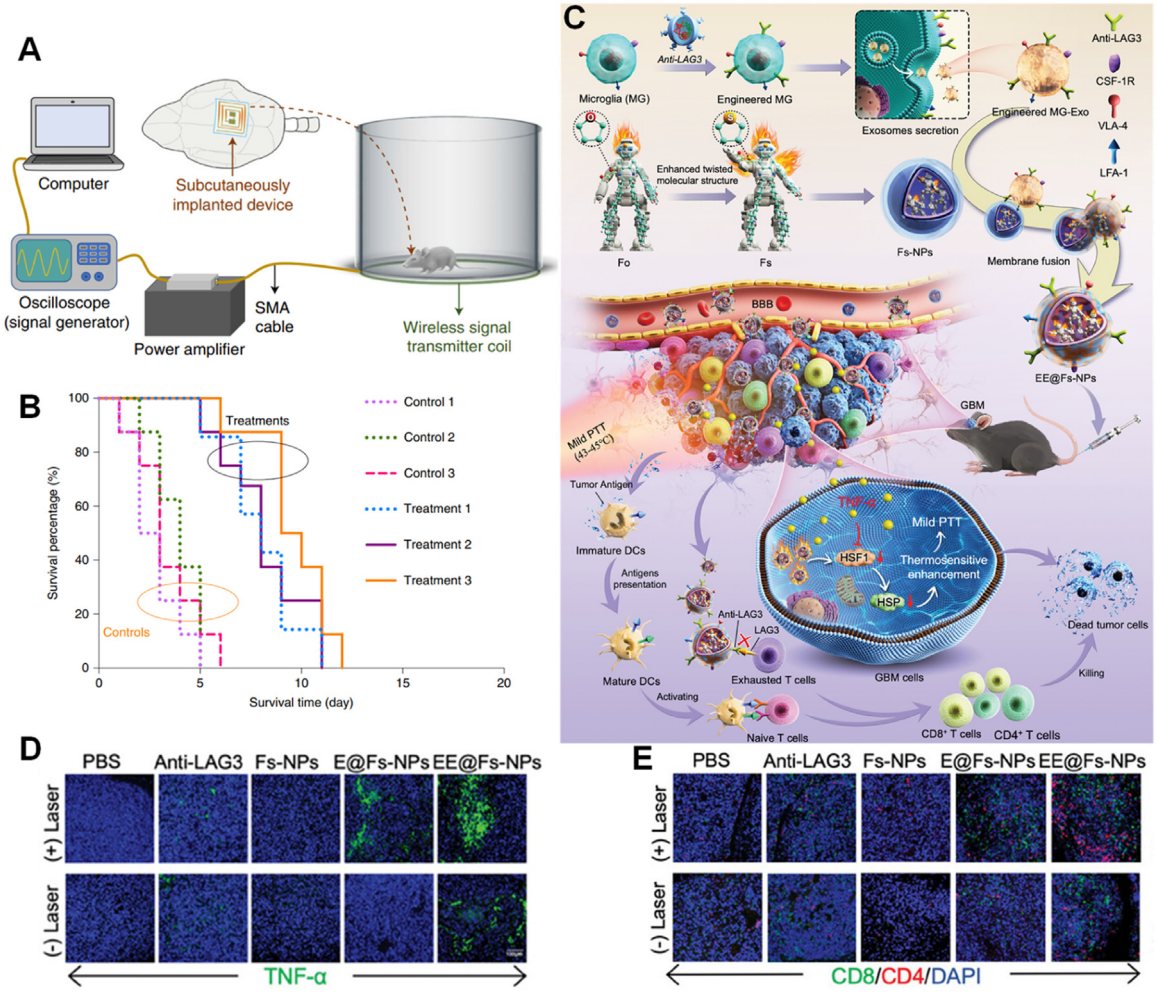


**Fig. 4 – (A) Schematic showing the computer-controlled wireless power supply device for PTT of GBM; (B) Survival curves of mice in treatment groups and control groups ($n$ = 10). Control 1: NPs(–), implantation(+); Control 2: NPs(+), microfibre(+), irradiation(–); Control 3: NPs(+), device(+), irradiation(–); Treatment 1: NPs(+), microfibre(+), irradiation (810 nm)(+); Treatment 2: NPs(+), 810 nm device(+), irradiation(+); Treatment 3: NPs(+), 940 nm device(+), irradiation(+) ($P$ <0.05, employing the log-rank test). Reproduced with permission from [86], Copyright 2022 Springer Nature Limited; (C) Schematic illustration of EE@Fs-NPs crossing BBB and delivering anti-LAG3 to GBM for mild PTT-ICB therapy; (D) Infiltration of TNF-$\alpha$ in GBM tumor tissues, assessed by immunofluorescence staining in different groups; (E) Infiltration of CD8$^+$ T cells and CD4$^+$ T cells in GBM tumor tissues, assessed by immunofluorescence staining in different groups. Reproduced with permission from [93], Copyright 2023 Wiley-VCH GmbH.**

[79]. A bacteria-nanoparticle hybrid system, comprising ICG-loaded and glucose polymer-bonded silicon nanoparticles, was developed for photothermal immunotherapy of glioma under NIR-I (808 nm) laser irradiation. The system could traverse the BBB and precisely target GBM tissue with Trojan bacteria assistance, exhibiting excellent conversion of light energy to heat to promote antitumor immunity [80]. In addition, Li et al. constructed an 'intelligent cell' using photothermal materials $Fe_3O_4$-Cy5.5-loaded macrophages for multimodal imaging and PTT. The primary macrophages, acting as drug carriers, could cross the BBB to target glioma. Effective ablation of glioma cells was achieved by the 'intelligent cell' that could distinguish brain tumor from normal tissue, using 808 nm NIR-I laser treatment with minor side effects [81]. In addition to PTAs with absorption in the NIR-I region, additional agents with strong NIR-II (1000–1700 nm) emission characteristics have become powerful tools for glioma treatment, offering high spatio-temporally controllability and sufficient penetration depth to pass through the skull [20,82-85]. Ultra-bright NIR-II conjugated polymer with AIE activity was synthesized by Tang et al. The polymer was wrapped with natural killer (NK) cell membrane for PTT, and was characterized by inhibition of tissue absorption and scattering. Polymers with NK cell properties could effectively penetrate the BBB and aggregate in glioma tissue to strongly inhibit tumor growth under laser irradiation [75]. Conventional optical therapy of brain tumors is limited by the need to expose the targeted tumors via dangerous open-skull surgeries, to activate a light-triggered response. As illustrated in Fig. 4A, Gambhir et al. developed

a novel nanomedicine-bioelectronics interface between brain and machine, that enables remotely controlled therapy with the properties of continuous, on-demand, and non-surgical intervention. Subcutaneous implantation of a wirelessly-powered light-emitting device on the skull was employed to irradiate gold nanostars with NIR surface plasmon features for precise PTT of deep-seated brain cancer [86]. Experimental evidence has shown that the treatment did not interfere with the usual activities of the mice, and no side effects or behavioral changes resulted from radiation, wireless power transmission, the presence of nanoparticles in glioma tissue, or photothermal heating of the glioma. By integrating state-of-the-art PTT with the latest advancements in bioelectronics, this system achieved effective and controlled PTT of glioma, resulting in prolonged survival of mice compared with the control group (Fig. 4B).

#### 2.2.3. *Non-inflammatory PTT*

The temperatures of PTT typically exceed 50 °C, resulting in tumor coagulation necrosis and triggering adverse inflammatory reactions. Inflammation induced by PTT often promotes tumor recurrence and metastasis, thereby diminishing treatment efficacy. Consequently, there is an urgent need to develop non-inflammatory or anti-inflammatory PTAs suitable for tumor photothermal ablation. Wang et al. utilized liquid exfoliation to prepare ultra-small zirconium carbide nanodots with an average diameter of approximately 4.5 nm. These nanodots were employed as PTAs for PTT, effectively ablating gliomas. Moreover, their outstanding ROS scavenging capability inhibited the harmful inflammatory response associated with PTT [87]. Chen et al. synthesized two-dimensional $Bi_2Se_3$ nanodisks with high photothermal stability and biocompatibility, whose multi-enzyme activity effectively suppressed the inflammatory response induced by PTT through their high capacity for scavenging ROS [88]. Injecting $Bi_2Se_3$ nanodisks into the tail vein of GL261 tumor-bearing nude mice, followed by external laser irradiation, effectively ablated tumors and alleviated the inflammatory response caused by heat damage post PTT.

#### 2.2.4. *PTT-derived multimodal synergistic therapy*

Standalone employment of PTT may not completely eliminate glioma cells, and its efficacy varies among individual patients. Multimodal synergistic therapies that integrate PTT with other treatment modalities have been extensively investigated over the past decade [89]. To facilitate more comprehensive treatment, a photoacoustic image-guided synergetic PTT/CDT has been developed using ultrasmall nanocrystals conjugated with lactate oxidase to enhance *in situ* $H_2O_2$ content, and coated with GBM cell membrane-based liposomes to penetrate the BBB and target orthotopic GBM. The high photothermal conversion efficacy of nanocrystal and the accelerated localized chemodynamic effect, due to the increased $H_2O_2$ content, could achieve outstanding therapeutic outcomes for GBM with negligible normal tissue toxicity [90]. Huang et al. constructed a targeted peptide-decorated mesoporous silica-wrapped graphene nanosheet combined with DOX for chemo-photothermal targeted therapy of glioma [91]. This multifunctional nanosheet enhanced uptake by glioma cells through receptor-mediated targeting, achieving effective inhibition of cell proliferation under NIR laser irradiation, surpassing the efficacy of chemotherapy or PTT alone. A differential PTT agent based on brain-targeting glycopeptide-29 peptide modified hybrid nanomaterials was proposed by Zhang et al., which embedded Ir nanozymes and pro-photothermal agent, 3,3′,5,5′-tetramethylbenzidine (TMB), on Gd-based nanodisks. The peroxidase (POD)-like activity of Ir nanozymes was activated by the acid and high concentration of $H_2O_2$ in TME, and further triggered chromogenic reaction amplification of TMB to initialize controllable PTT, whereas the TMB remained silent and the harmful ROS was scavenged in normal brain tissue. Thus, the nanomaterials could act as an autophagy inhibitor to enhance the PTT effect and alleviate inflammation to protect normal tissue [92].

PTT has the potential to stimulate the immune system of body to recognize tumor-associated antigens and promote infiltration of T cells into the TME. Hence, combining PTT with immunotherapy has gained attention in the field of glioma treatments. Deng et al. proposed a synergistic therapy that utilizes microglia-exosomes expressing immune checkpoint LAG3 inhibitory antibody (anti-LAG3) to encapsulate PTA AIE for photothermal-immune treatment (Fig. 4C) [93]. The external engineered microglia-exosomes demonstrated the ability to facilitate the crossing of the BBB and target GBM, effectively delivering anti-LAG3 and PTA to GBM cells. As shown in Fig. 4D and E, the results demonstrated that Anti-LAG3 significantly reverses T cell exhaustion and induces the production of TNF-$\alpha$, thereby inhibiting the expression of heat shock proteins and enhancing the thermosensitivity of tumor cells. And PTA AIE further enhanced the infiltration of cytotoxic $CD8^+$ *T* cells by the production of mild PTT in GBM, thereby augmenting the responsiveness of immune checkpoint blockade therapy to achieve more efficient glioma ablation.

### 2.3. *Synergistic phototherapy (PDT and PTT)*

Under laser irradiation controlled in both spatial and temporal dimensions, integrating PDT and PTT into one theranostic system, which harnesses the tumor-destructive effects of generated ROS and localized heat, was regarded as a potential treatment approach [29,94,95]. Qi's group designed a catalase-integrated albumin nanoprobe loaded with gold nanorods and ICG for combined phototherapy and multimodal imaging [96]. This system converted endogenous $H_2O_2$ into oxygen by catalase to power PDT, while the localized hyperthermia and high ROS levels in the brain promoted glioma cell apoptosis and extended survival time of tumor-bearing mice. Shirvalilou et al. engineered functionalized acrylic copolymer nanomaterials with spiropyran and imidazole groups by semicontinuous emulsion polymerization, in which $Au^{3+}$ ions were reduced on the surface for phototherapy [97]. The gold nanoparticles embedded in the polymer not only enhanced the photogeneration of ROS through spiropyran-merocyanine photoisomerization but also increased local photothermal efficiency after irradiation in glioma cells. Furthermore, NIR phototherapy based on Tm-doped upconversion nanoparticles (UCNPs) was designed to enhance the penetration of theranostic through the skull for

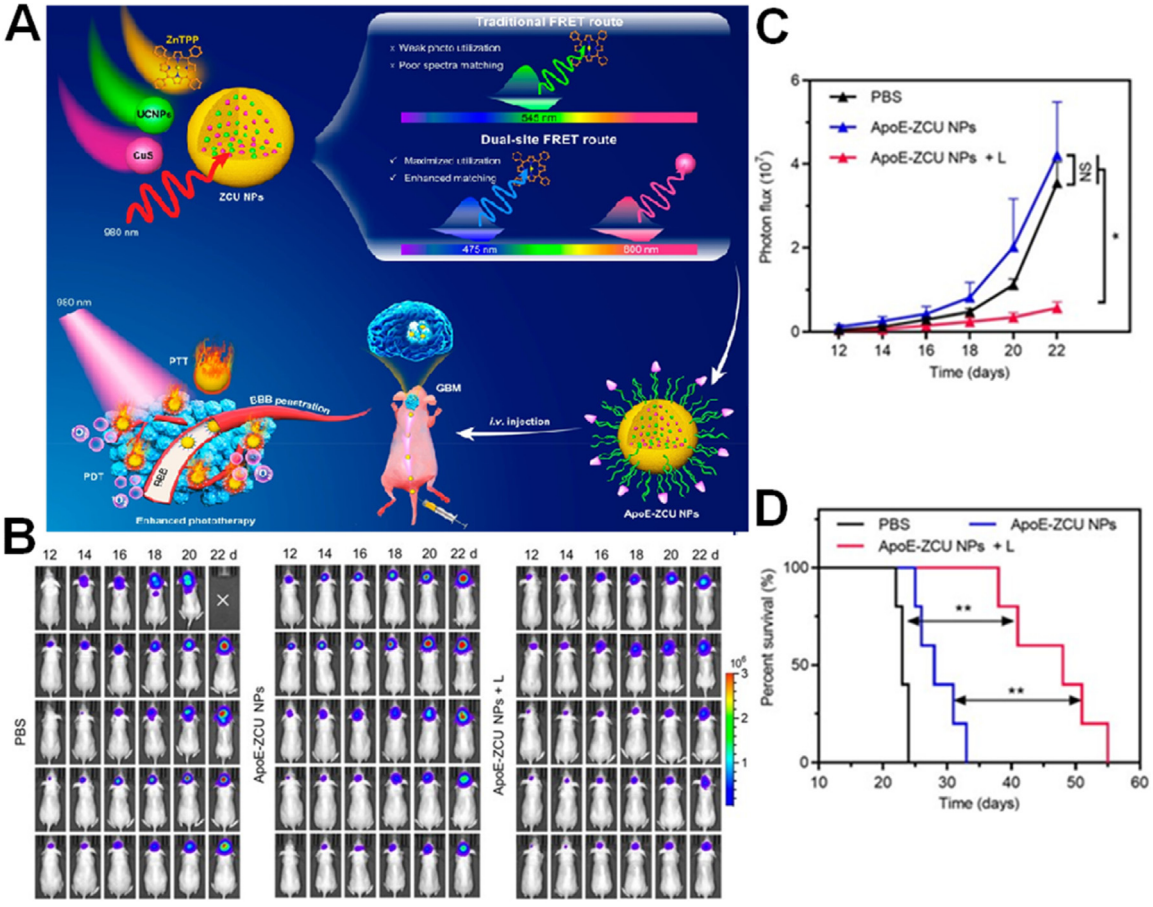


**Fig. 5 – (A) Illustration for the advantage of dual-site FRET routes of ApoE-ZCU NPs compared to traditional FRET in brain-target phototherapy. (B) Bioluminescence images of glioma-bearing mice in different groups and (C) the corresponding quantified intensity of the tumor as a function of time. (D) Survival curves of the mice. Data are shown as the mean ± SEM, NS indicates no significance, *P < 0.05, **P < 0.01. Reproduced with permission from [98], Copyright 2023 American Chemical Society.**

promising GBM phototherapy (Fig. 5A). The emission of UCNPs under 980 nm laser irradiation prompted the downstream PSs copper sulfide nanocrystals and porphyrin for PTT and PDT via Förster resonance energy transfer (FRET), and the ratio of Tm-doping in UCNPs was adjusted to acquire superior FRET spectral matching by structure and spectral modulations [98]. The bioluminescence images of glioma confirmed significant inhibition in the UCNPs group under localized laser irradiation (Fig. 5B and 5C). The treatment extended the survival time of in mice bearing glioma to 55 d, surpassing both the PBS group (24 d) and the non-irradiated group (33 d) (Fig. 5D). These rationally designed therapeutic systems exhibited great promise for spatio-temporally controllable phototherapy of glioma.

## 3. Sono-based spatio-temporally controllable glioma therapy

SDT relies on low-intensity US, oxygen, and sensitizing drugs to induce therapeutic effects, similar to PDT, but differs in using US instead of light to stimulate the sensitizers [99]. With its advantages of accurate spatio-temporally control, non-invasiveness, and considerable tissue penetration depth, SDT has been identified as an attractive approach for enhancing targeted therapeutic efficiency in glioma treatment [100,101]. US, defined as mechanical waves with frequencies above the audible range, can pass through different substances, including tissue, liquids and gases, without causing harm to living organisms, proving especially advantageous for treating glioma [16]. After combining US and sensitizers in the brain, their interaction is exploited to induce apoptosis in glioma cells [102]. Thus, by providing deeper penetration through intervening in tissue and boosting the permeability of blood vessels and cell membranes, SDT offers significant potential for successful application in glioma therapy.

### 3.1. *Types and delivery of sonosensitizers*

Several sonosensitizers have been utilized to demonstrate the effects of SDT on glioma, including sinoporphyrin, photofrin, and hematoporphyrin mono-methil ether [103-105]. In addition, 5-ALA and Ce6, commonly used in PDT, have also been used as sonosensitizers [24-26]. In 2011,

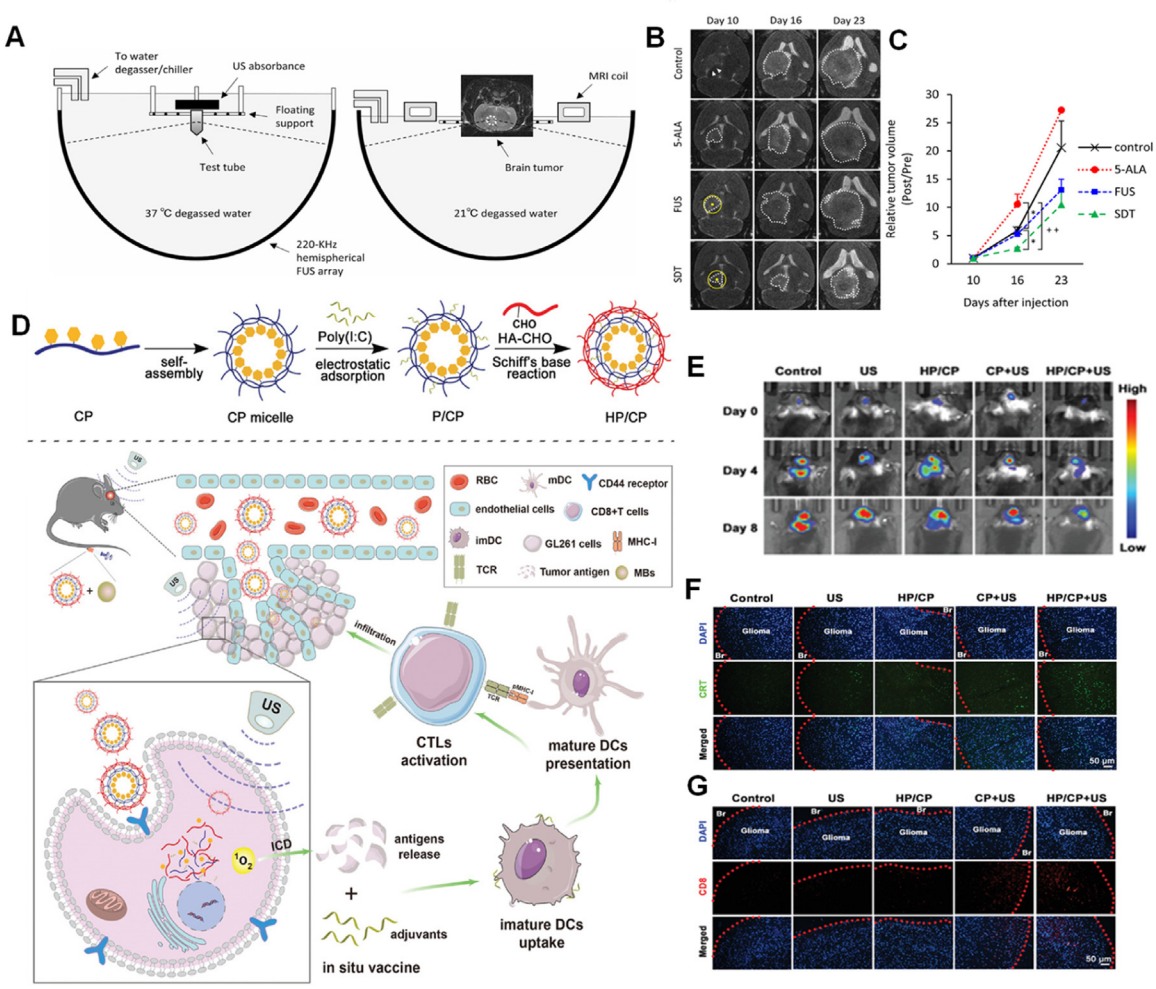


**Fig. 6 – (A) Schematic illustration of MRI-guided FUS combined with 5-ALA for SDT; (B) T2-weighted images of F98 tumor (arrowhead, white dotted line) from Days 10 to 23. The yellow circle and dot mark the rise in temperature at the target site; (C) Tumor progression in different groups-control, 5-ALA, FUS group, and SDT-from Days 10 to 23 (Reproduced with permission from [107], Copyright 2018 World Federation for Ultrasound in Medicine & Biology); (D) Schematic illustration of the design of HA-Poly(I:C)/COS-PpIX nanosonosensitizer and sono-immunotherapy of glioma; (E) Bioluminescence images of mice bearing orthotopic GBM after various treatments on Days 0, 4 and 8; (F) Expression of CRT and (G) the infiltration of $CD8^+$ T cell in brain tumor tissue sections, assessed by immunofluorescence staining after different treatments. The red dotted line marks the boundary between GBM and normal brain tissue. Scale bar: 50 μm (Reproduced with permission from [111], Copyright 2022 Wiley-VCH GmbH).**

Umemura et al. utilized 5-ALA with focused ultrasound (FUS) to treat glioma-bearing rats for the first time, proving that SDT is a powerful tool for treatment of deep malignant glioma [106]. Furthermore, Houkin et al. used transcranial clinical magnetic resonance imaging (MRI) to assist SDT with 5-ALA in a facility authorized for high-intensity FUS ablation (4,000 J, 20 W, 240 s) (Fig. 6A) [107]. The resulting ROS strongly inhibited glioma proliferation and invasion without harming the surrounding normal tissue. Evidence from MRI and tumor progression curves demonstrated that gliomas treated with a combination of 5-ALA and FUS exhibited delayed growth (Fig. 6B and 6C).

Xu et al. evaluated the effects of SDT against glioma *in vivo* and *in vitro* using fluorescein, a biosafe xanthene dye known for its fluorescent properties and ability to selectively exit normal tissue and aggregate in brain tumors [102]. The singlet oxygen produced by the interaction of fluorescein with an ultrasonic field significantly inhibited the growth of ectopic glioma, and this trend was observed using TUNEL and active caspase-3 staining assays in glioma-bearing models. Porphyrin-based sonosensitizers have also attracted considerable attention in the context of glioma treatment [108-110]. For example, Liu et al. employed sinoporphyrin sodium as a sensitizer for SDT, examining US parameters to enhance BBB permeability and its inhibitory effect on glioma cells [103]. Guan et al. used the sonosensitizer protoporphyrin IX, conjugated with chitosan oligosaccharide (COS), and electrostatically adsorbed the immune-enhancing adjuvant Poly(I:C) to achieve nanosonosensitizer-augmented sono-immunotherapy, then linked with hyaluronic acid to target and accumulate in the GBM tissue (Fig. 6D) [111]. The nanoparticles effectively and non-invasively opened the

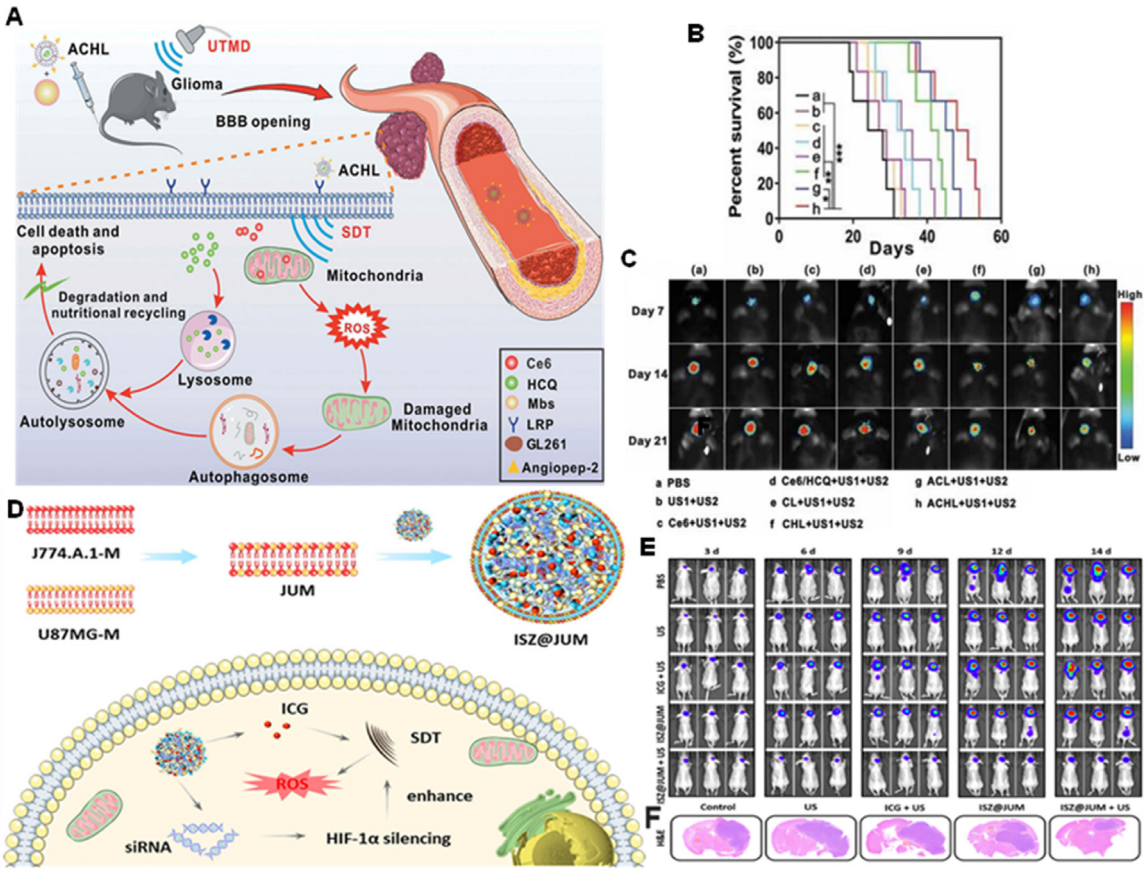


**Fig. 7 – (A) Schematic illustration of ACHL nanosensitizer platform used to cross the BBB and achieve precision SDT; (B) Survival curves of GL261-bearing mice in different groups ($n = 6$), data are presented as mean ± SD. *P < 0.05, **P < 0.01, ***P < 0.001; (C) Bioluminescent signals correlating to tumor growth over time. (Reproduced with permission from [115], Copyright 2019 Taylor & Francis); (D) Schematic illustration showing how ISZ@JUM crossed the BBB to target gene silencing and enhanced SDT of GBM; (E) Representative bioluminescence images of U87 tumor-bearing mice across all groups; (F) H&E staining images of brain sections of U87 tumor-bearing mice in all groups. Scale bar: 100 μm. Reproduced with permission from [118], Copyright 2023 American Chemical Society.**

BBB and produced ROS in response to acoustic sensitization, augmenting the immunogenicity of the GBM. When combined with the released adjuvant Poly(I:C), it had the potential to create an in-situ vaccine at the glioma site, stimulating T-cell-mediated immune responses for effective GBM ablation. Under US activation, the material efficiently suppressed the growth of *in situ* GBM (Fig. 6E). Targeted by hyaluronic acid (HA), the nanosonosensitizer induced a stronger immunogenic cell death (ICD) effect on GBM cells, followed by a vaccine effect from the combination of antigens generated by ICD and immunoadjuvants, recruiting more cytotoxic T cells to achieve sono-immunotherapy therapy of GBM (Fig. 6F and 6G).

### 3.2. *Microbubbles (MBs)*

MBs combined with transcranial-focused US offer a noninvasive and reversible method for opening the BBB at specific locations, creating a temporary time frame for enhancing the delivery of therapeutic substances into brain tissue. MBs play a crucial role in this process by interacting with US energy, enhancing acoustic effects and microstreaming, which leads to mechanical stress that activates transient morphological deformation of tight junctions [112]. Additionally, MBs can serve as vehicles for drugs, enhancing US-mediated drug delivery by releasing drugs only upon sonication, thereby improving the precision and efficacy of drug release [113,114].

Qu et al. utilized an US-targeted MBs disruption technique to open the BBB for targeted nanosonosensitizer delivery in glioma region. The fabricated nanosonosensitizer could penetrate the BBB to achieve spatio-temporally controllable glioma therapy under the action of US (Fig. 7A) [115]. Initially, an US pulse (US1) was administered to open the BBB, followed by the injection of liposomes. Subsequently, a second continuous US pulse (US2) was applied 36 h later to induce drug release from the liposomes, achieving temporally controllable therapy. The loaded sonosensitizer Ce6 generated ROS under US irradiation, leading to cell apoptosis, while simultaneously releasing hydroxychloroquine-inhibited autophagosome degradation, amplifying ROS generation within the tumor. *In vivo* treatment evaluation demonstrated

that the nanosonosensitizer significantly inhibited tumor growth and extended the median survival time of glioma-bearing mice (Fig. 7B and 7C).

### 3.3. *Oxygen*

Exploiting oxygen-supplying methods to alleviate tumor hypoxia and boost oxygen content within glioma tissue is also crucial for effective SDT [116]. Wang et al. employed a mild biomineralization method to grow $MnO_2$ nanocrystals on holo-transferrin (Tf), which can cross the BBB via receptor-mediated transcytosis. Under low pH and high GSH conditions, the generated oxygen via $MnO_2$ improved the SDT effect of the sonosensitizer protoporphyrin, and the subsequent released $Mn^{2+}$ was conducted for specific MRI-synergistic SDT of GBM [108]. Catalase combined with ICG was also used to develop highly effective oxygen-enhanced SDT against GBM [117]. The modulation of vital transcriptional regulators of hypoxia in the TME is also a desirable strategy to improve the efficacy of SDT for glioma. Cao et al. selected HIF-1$\alpha$ small interfering RNAs (siRNAs) to block the HIF-1$\alpha$ expression in glioma cells for ameliorating of hypoxic environments (Fig. 7D) [118]. The pH-sensitive release of ICG and HIF-1$\alpha$ siRNAs in ZIF-8 nanoparticles achieved superior SDT, indicating the significant role of relieving hypoxia in improving the SDT efficacy. In the monitoring via bioluminescence images and examination of brain tumor tissues from mice stained with hematoxylin and eosin (H&E), it was observed that the group treated with siRNAs demonstrated significant tumor suppression (Fig. 7E).

### 3.4. *SDT-derived multimodal synergistic therapy*

Compared to monotherapy with SDT, integrating two therapeutic agents in a single material can achieve striking superadditive therapeutic effects. Synergistic sonodynamic/chemotherapeutic systems are commonly constructed to compensate for the monotherapy of glioma. As illustrated in Fig. 8A, Zong et al. designed a stimulus-responsive nanoparticle conjugated to the chemotherapeutic drug paclitaxel (PTL) using ROS-cleavable thioketal ligands by a hydrophilic and hydrophobic action, with the sonosensitive agent IR780 installed in the hydrophobic core for SDT [119]. Upon FUS irradiation, ROS produced by SDT could both directly induce glioma cell apoptosis and promote the release of PTL from nanoparticles, achieving controlled synergistic sono-chemotherapy. As illustrated in Fig. 8B and 8C, the combination of sonosensitive and PTL exhibited the greatest inhibitory effect on tumor growth under US irradiation. And the graph of mouse weight demonstrated that the nanoparticle exhibited no significant toxicity, indicating its safety as a treatment modality. Chemotherapy is a vital and complementary clinical therapeutic method for patients with glioma; however, high levels of chemoresistance greatly limit its application. Thus, Cai et al. developed a biodegradable and pH-sensitive nanosystem with homologous targeting ability, in which ROS generation by the sonosensitizer DOX not only promoted GBM cell apoptosis but also down-regulated chemoresistance-related factors to reverse resistance and increase sensitivity to drug for sonodynamic-enhanced chemotherapy [120]. Recently, a novel cell death pathway dependent on copper, termed cuproptosis, has been discovered. Kang et al. constructed a carrier-free nanoparticle (Ce6@Cu NPs) through self-assembly by coordinating $Cu^{2+}$ ions with sonosensitizer Ce6 (Fig. 8D) [121]. In glioma cells, Ce6@Cu NPs exhibited excellent sonodynamic effect under US irradiation, generating abundant ROS, which further led to the oxidation of polyunsaturated fatty acids (PUFA), subsequently triggering lethal lipid peroxidation (LPO). The GSH depletion ability of Ce6@Cu NPs further promoted LPO, ultimately inducing ferroptosis. The reaction between $Cu^{2+}$ and reductive GSH increased the concentration of $Cu^{+}$ in the glioma cells, leading to irreversible cuproptosis. *In vivo* experiments demonstrated that mice treated with Ce6@Cu NPs plus US irradiation exhibited the lowest tumor proliferation rate due to the synergistic effects of sonodynamic therapy, ferroptosis, and cuproptosis (Fig. 8E and 8F).

## 4. Radio-based spatio-temporally controllable glioma therapy

In the past few decades, RT has become a major and well-established non-surgical treatment used against glioma in clinic, with nearly all glioma patients undergoing RT. Ionizing radiation used in RT includes photon radiation (X-rays and gamma rays) and particle radiation (alpha particles, heavy ions, protons, etc.) [5,13]. During RT, photon or ion radiation interacts with the medium, depositing energy, and then tumor cells are damaged via ionization of DNA fragments or production of low-energy electrons or free radicals [122]. In recent years, new research about different durations, doses, or formulas of RT are being reported continuously [123-126]. Unlike most phototherapies, RT offers unlimited penetration depth in the organism with spatio-temporally controllability, making it a prominent glioma treatment option [127].

### 4.1. *Delivery of radio-agents*

Targeted delivery of radio agents to specific locations of gliomas is critical for achieving spatio-temporally controllable RT. Benoit et al. designed $^{188}$Re-loaded lipid nanoparticles to be given RT for glioma, either by convection-enhanced delivery alone or combined with a simple stereotactic injection for direct drug distribution into the brain [128,129]. Improvements in the median survival time of mice and enhancement of the immune response *in vivo* proved that this treatment was effective against glioma. Recently, the use of radio agents coupled with appropriate reagents (peptide, antibody, and nanocarrier) for internally enhanced glioma RT has attracted considerable attention due to their excellent targeting and aggregation abilities [130-135]. As illustrated in Fig. 9A, Liu et al. utilized a nano-MOF to label the radio-nuclide lutetium-177 ($^{177}$Lu) and load fluorescent dye sulfo-cyanine7 (Cy7), achieving a promising theranostic approach combining imaging and RT [136]. The modification of nano-MOFs with folic acid enabled targeted delivery to tumor site, facilitating highly sensitive *in vivo* imaging and targeted RT of gliomas. Labeled $^{177}$Lu served as complementary probes

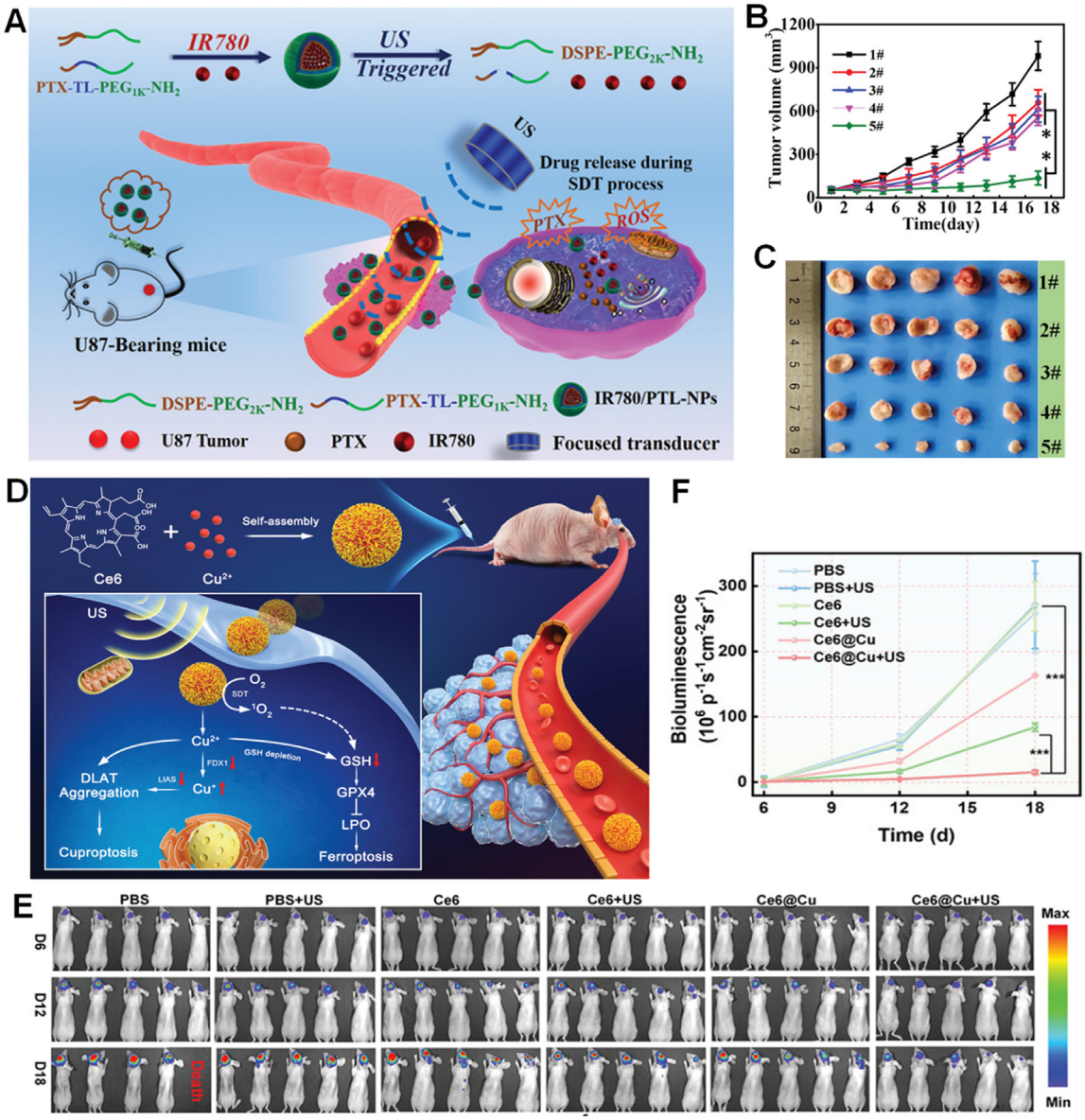


**Fig. 8 – (A) Schematic illustration of the synthesis and sono-chemotherapy of IR780/PTL nanoparticles; (B) Tumor volumes in different groups. **P < 0.01; (C) Representative photographs of tumors after various treatments. (Reproduced with permission from [119], Copyright 2019 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim); (D) Schematic illustration of the design and the sonodynamic-enhanced cuproptosis-ferroptosis of Ce6@Cu NPs in GBM therapy; (E) Bioluminescence images of orthotopic U87MG-Luc tumor-bearing mice with various treatments and (F) corresponding bioluminescence signals at Days 12 and 18. ***P < 0.001 (Reproduced with permission from [121], Copyright 2024 Wiley-VCH GmbH).**

to calibrate the cancer-binding affinity of the nanocarriers as indicated by fluorescence imaging, offering more precise biodistribution information (Fig. 9B). The utilization of TUNEL, Caspase-3, and Ki67 assays revealed the pro-apoptotic effect, proliferation inhibition, and DNA damage induced by the designed nanomaterial on tumor cells (Fig. 9C).

### 4.2. *Radiosensitization*

High-dose radiation in brains with glioma may be associated with brain damage and increased fatality rates [137]. Consequently, development of specific strategies to optimize the efficacy of low-dose RT of glioma is crucial [135,138]. It is reported that high atomic number (Z) materials, such as noble metals and semiconductor materials, are frequently utilized to sensitize cancers to RT on account of amplifying energy deposition [139]. Larger surface areas of small particles also increase secondary radiation scattering, concentrating energy in the tumor region [140]. Zhang et al. constructed small-sized pharmaceutics composed of Au sub-nanometer particles, cell cycle regulator $\alpha$-difluoromethylornithine (DFMO) and BBB penetration peptide iRDG for sensitizing RT [141]. The release of DFMO through tumor cell apoptosis induced by initial radiation treatment appeared to render

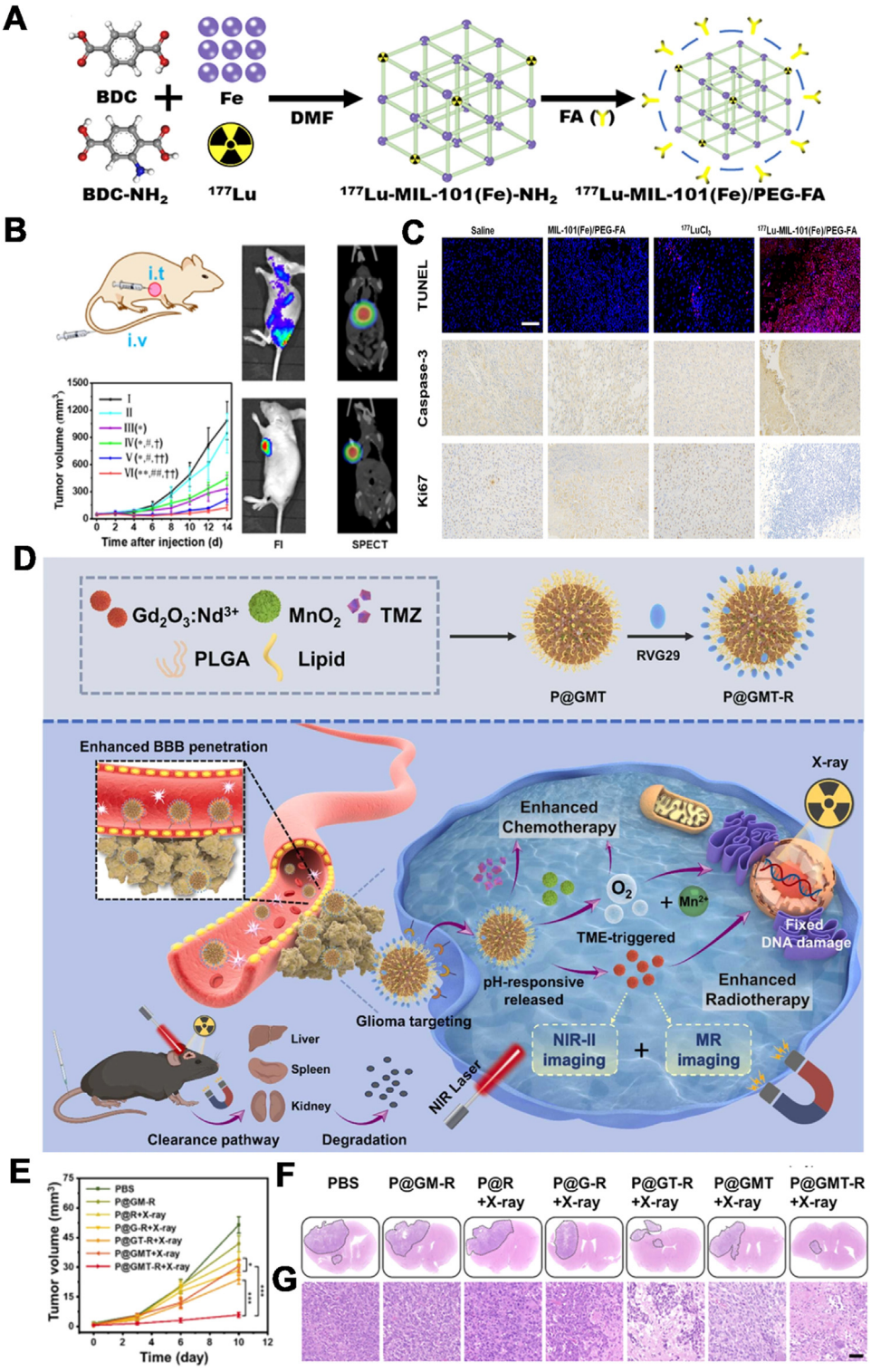


**Fig. 9 – (A) Illustration of the design of $^{177}$Lu-MIL-101(Fe)/PEG-FA; (B) $^{177}$Lu-MIL-101(Fe)/PEG-FA was designed for high-sensitive imaging and targeted radiotherapy of glioma; (C) Immunofluorescence staining of excised tumor tissues for TUNEL, caspase-3, and Ki67 on Day 6 after different treatments; Scale bar: 100 μm. (Reproduced with permission from [136], Copyright 2023 American Chemical Society); (D) Illustration of the synthesis and theranostics of $Gd_2O_3$ nanodot; (E) Tumor volumes of glioma in different groups of mice; (F) Histological evaluation of glioma tumor burden (outlined with black dotted lines) at the termination of the study in mice subjected to various treatments; (G) H&E staining images of tumor sections from each group after various treatments. Scale bar: 50 μm. (Reproduced with permission from [142], Copyright 2022 Elsevier Ltd).**

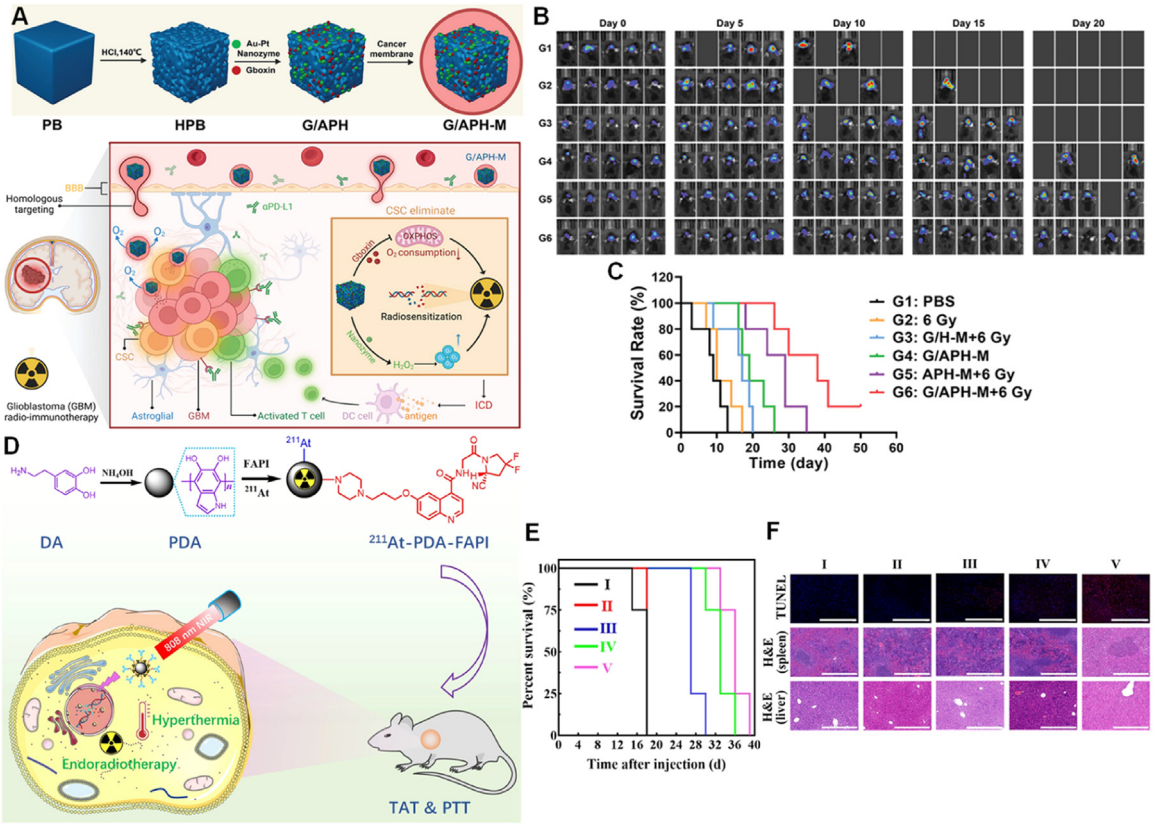


**Fig. 10 – (A) Illustration of the synthesis of G/APH-M and its combination with anti-PD-L1 to enhance radio-immunotherapy of GBM; (B) IVIS images showing bioluminescence from GBM in mice on Days 0, 5, 10, 15 and 20 after different treatments. Blank areas indicate the dead mouse; (C) Survival curves of GBM-bearing mice in different groups. (Reproduced with permission from [19], Copyright 2023 Wiley-VCH GmbH); (D) Illustration of the synthesis of $^{211}$At-PDA-FAPI and its application in synergistic targeted alpha therapy and PTT for the treatment of malignant tumors; (E) Survival curves of U87MG-bearing mice in different groups; (F) Images of TUNEL-stained tumor sections 15 d post-injection and H&E-stained spleen and liver sections after various treatments (I: saline, II: PDA-FAPI nanoparticles, III: PDA-FAPI with laser irradiation, IV: $^{211}$At-PDA-FAPI without laser irradiation, and V: $^{211}$At-PDA-FAPI with laser irradiation). Scale bar: 500 μm. (Reproduced with permission from [162], Copyright 2024 American Chemical Society).**

GBM more sensitive to a second radiation treatment with minimal-dose RT. In addition, Zhang et al. selected $Gd_2O_3$ nanodot with high-Z Gd, which act as a contrast agent for MRI and luminescence material for NIR-II imaging and also as an RT sensitizer for efficient diagnosis and treatment against deeper glioma (Fig. 9D) [142]. The $Gd_2O_3$:$Nd^{3+}$ nanodots co-encapsulated $MnO_2$ and TMZ within poly(lactic-co-glycolic acid) (PLGA) were surface-modified with rabies virus glycoprotein, facilitating efficient BBB penetration and deep glioma accumulation. Precise RT was achieved using spatially and temporally controllable X-ray irradiation upon reaching the desired location. Simultaneously, the nanoparticles released TMZ and oxygen under the stimulation of TME, thereby enhancing the effectiveness of chemotherapy/RT. Under X-ray irradiation, the nanoparticles achieved optimal inhibition of tumor growth (Fig. 9E). H&E staining of the nanoparticle + X-ray group exhibited extensive necrosis and reduction in visible nuclei, providing additional evidence for the outstanding anti-glioma effectiveness of the design nanoparticle (Fig. 9F and 9G).

### 4.3. *Oxygen*

Hypoxia in the glioma core region may reduce the efficiency of RT, and the degree of hypoxia in glioma before RT is closely related to the patient overall survival [143,144]. Improving the hypoxic microenvironment of tumor cells is of significant importance for RT. For example, Yu et al. enhanced sensitivity to RT by combining nitroimidazole, a radiation sensitizer mimicking the role of oxygen in the radiochemical process, with DNA repair inhibitor Dbait in lipid molecules [145]. Liu et al. developed a nanoplatform (G/APH-M) to improve chemotherapeutic sensitivity and DNA damage in glioma cells when exposed to X-ray radiation. They achieved this by creating self-assembled lipid molecules with a small size that could effectively penetrate the BBB. The nanoplatform was prepared through in-situ reduction of Au-Pt nanozymes with catalase-mimetic activity, loading the phosphatase inhibitor Gboxin, and coating with cancer cell membranes on hollow Prussian blue (Fig. 10A) [19]. Inhibiting mitochondrial oxidative phosphorylation to reduce oxygen

consumption and increasing oxygen levels with nanozymes could simultaneously enhance RT. Bioluminescent imaging of mice revealed that RT alone had minimal impact on inhibiting the growth of refractory GBM (Fig. 10B and 10C). Furthermore, combining G/APH-M with 6 Gy of RT significantly suppressed the growth of GBM, and prolonged the survival of GBM-bearing mice, alleviating tumor hypoxia.

### 4.4. *Boron neutron capture therapy (BNCT)*

BNCT is an unconventional particle RT form that selectively destroy tumor cells containing $^{10}$B while sparing normal cells [146]. Under irradiation, $^{10}$B atoms in the selected cells transform into radioactive $^{11}$B after capturing low-energy thermal neutrons. And a fission reaction ensues with the release of highly linear energy transfer alpha particles and the recoil of $^{7}$Li nuclei for non-invasive treatment within 5–9 μm range [147,148]. Xing et al. designed a carbon dot constituted from D-glucose and L-aspartic acid involving $^{10}$B for targeted BNCT of glioma cells under neutron radiation [149]. The authors took advantage of the boron phenylalanine and D-glucose in carbon dots to target the L-amino acid transport system and glucose receptor in glioma cells, respectively, and further coated the dots with the exosomes of macrophages, increasing the cyclic time *in vivo* for efficient ablation of glioma. Apart from precisely targeted delivery of boron-compound drugs to tumor tissue, boron dose is also a significant factor requiring consideration during BNCT. In recent years, numerous different materials have been prepared to deliver sufficient quantities of boron to brain tumor sites, such as layered double hydroxide and MOF [148,150]. Hwang et al. demonstrated a novel $^{10}$B-enriched nanomedicine with 96% abundance, capable of delivering high doses of atomic boron to tumor areas [151]. This nanomedicine exhibited an exceptionally good tumor-to-blood boron ratio above 3.0, enabling non-invasive GBM BNCT. Compared with the control group, mice injected with the synthesized nanomedicine and exposed to neutron irradiation exhibited a significant delay in tumor volume. Nakamura et al. also exploited a novel FR$\alpha$-targeting and albumin-binding $^{10}$B agent consisting of pteroyl–closo-dodecaborate moiety, in which the $^{10}$B resource contains twelve $^{10}$B atoms per molecule [152]. Intravenous injection of $^{10}$B achieved high accumulation of 29.8 μg [$^{10}$B]/g in glioma tissue at 6 h, enhancing therapeutic efficacy after controllable thermal neutron irradiation.

### 4.5. *Targeted alpha therapy and other radiation technologies*

Targeted radionuclide therapy offers significant advantages in treating malignant gliomas, such as beta or Auger electron therapy, by delivering high-dose radiation to the tumor site while preserving surrounding healthy tissues. The high cytotoxicity of DNA double-strand breaks, the bystander effect, and the secondary cross-dose effect make alpha radiation therapy particularly effective [153]. $^{213}$Bi, $^{211}$At, and $^{255}$Ac have been frequently used to investigate targeted therapy in gliomas [154-160]. Maris et al. have demonstrated the safety and antitumor activity of [$^{211}$At]meta-astatobenzylguanidine ([$^{211}$At]MABG) in a preclinical model of neuroblastoma. They also compared the anticancer effects of [$^{211}$At]MABG and [$^{131}$I]meta-iodobenzylguanidine ([$^{131}$I]MIBG) in three mouse xenograft models. The results showed a significant survival advantage with [$^{211}$At]MABG in the disseminated neuroblastoma model, indicating its potential for clinical development [161]. Furthermore, Liu et al. engineered polydopamine (PDA) nanoparticles modified with $^{211}$At and fibroblast activation protein inhibitor (FAPI), enabling synergistic targeted alpha therapy and PTT of glioma (Fig. 10D) [162]. Compared with the control group, this therapeutic approach extended the median survival of tumor-bearing mice by twofold, from 18 d to 36 d, with negligible toxicity observed in the mouse model (Fig. 10E and 10F). In addition, other RT techniques, such as helical tomotherapy, intensity-modulated RT, and volumetric-modulated arc therapy, have also been demonstrated to enhance the therapeutic efficacy of glioma [163,164].

### 4.6. *RT-derived multimodal synergistic therapy*

Presently, the primary clinical approach for treating glioma involves maximal surgical resection followed by combined RT and chemotherapy. Therefore, it is appealing for extensive research into radio-chemotherapy [142,165]. Moreover, RT induces immunogenic cancer cell death by causing extensive DNA damage, resulting in the release of DNA and RNA, which stimulate the immune system against tumors. This inherent characteristic forms the basis for combining RT with immunotherapy [166]. Zhong et al. utilized a disulfide-crosslinked chimeric biodegradable polymers modified with apolipoprotein E peptide to achieve effective brain delivery of CpG [167]. Upon BBB penetration and glioma site targeting, the intracellular redox-triggered release of CpG stimulated the maturation of dendritic cells, antigen cross-presentation, and the generation of pro-inflammatory cytokines. Integrating the designed polymers with RT further enhanced immunotherapy for glioma. Additionally, it has been indicated that tumor-associated macrophage-like cells (TAMCs) are recruited in large numbers to GBM in response to RT, leading to increased expression of PD-L1 and compromised anti-tumor immune response. As shown in Fig. 11A, Tannous et al. employed extracellular vesicles (EVs) as therapeutic delivery carriers modified with siRNA (RGD-EV:siPDL1) for RT-primed immune checkpoint treatment [168]. The surface of used EVs modified with RDG peptide was equipped to target GBM cells for deeper synergistic spatio-temporally controllable RT. And loaded siRNA not only reversed radiation-induced PD-L1 expression on GBM cells but also recruited TAMCs, leading to a synergistic effect. Co-therapy of RT and RGD-EV:siPDL1 remarkedly downregulated the abundance of $CD8^+$ *T* cells and profoundly enhanced mean fluorescence intensity of three markers (IFN-$\gamma$, TNF-$\alpha$, and Granzyme B) of $CD8^+$ *T* cells, while RT alone facilitated the infiltration of the immunosuppressive cells (Fig. 11B-11D). Fluorescence bioluminescence imaging demonstrated that mice treated with RT + RGD-EV:siPDL1 exhibited a significant impact on tumor growth (Fig. 11E and 11F). These combined approaches of RT and immunotherapy showed significant promise for clinical translation in improving glioma treatment.


**Fig. 11 – (A) Schematic illustration of targeted extracellular vesicles for RT of glioma; (B) The abundance of CD8$^+$ T cells ($n$ = 6); (C) Representative zebra plots showing the expression of IFN-$\gamma$, TNF-$\alpha$, and Granzyme B on tumor-infiltrating lymphocyte CD8$^+$ T cells in GBM; (D) Efficient function of tumor-infiltrating lymphocyte CD8$^+$ T cells quantified by the percentage of IFN-$\gamma^+$, TNF-$\alpha^+$ and Granzyme B$^+$ populations and their mean fluorescence intensity ($n$ = 6); (E) Fluc bioluminescent signal correlating to tumor growth over time; (F) Quantification of tumor-associated Fluc radiance intensity after different treatments. Data presented as mean ± SEM; *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001. (Reproduced with permission from [168], Copyright 2022 American Chemical Society).**

## 5. Magnet-based spatio-temporally controllable glioma therapy

Magnetic fields offer spatio-temporally controllability and high biological penetration depth, making them a promising non-invasive physical technique for biomedical applications. The fields can induce effects such as hyperthermia and mechanical force, which are particularly useful in treating glioma. Magnetic hyperthermia therapy (MHT) is gaining prominence as an alternative therapy to supplement traditional glioma treatments [169-173]. Conventional MHT is achieved through three distinct mechanisms: hysteresis loss, Brownian and Néel relaxation, which generate heat energy upon stimulation [174,175]. Utilizing biocompatible external permanent magnets to attract magnetic materials to tumor tissues, leading to protein denaturation, DNA damage, signal interruption, cell growth inhibition, and apoptosis, represents a promising therapeutic approach [176]. Furthermore, the contactless application of alternating magnetic field (AMF) makes MHT a controllable remote treatment, capable of targeting tumors that are inaccessible to phototherapy. Therefore, magnetic agents capable of converting magnetic energy into heat in response to AMF can be a valuable option for treating certain cancers located near vital organs, particularly brain tumors.

### 5.1. *MHT*

The most commonly employed magnetic materials for MHT are superparamagnetic $Fe_3O_4$ NPs, renowned for their robust

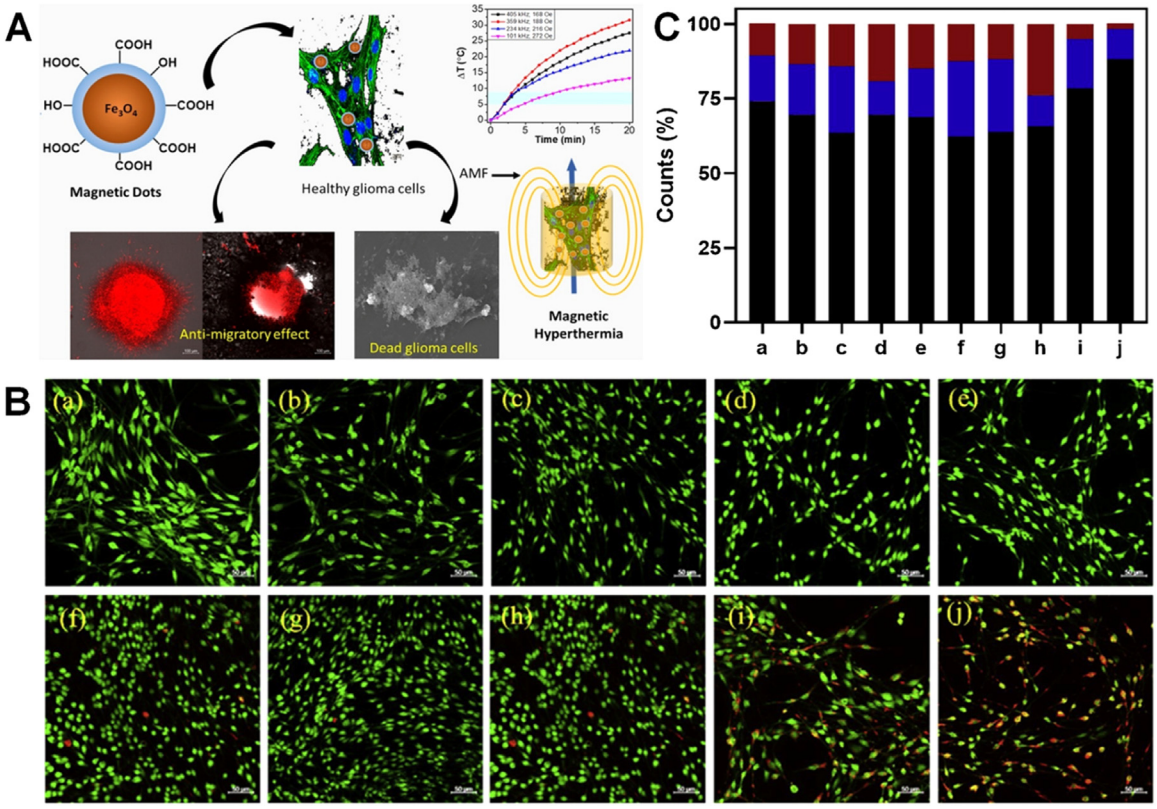


**Fig. 12 – (A) Illustration of the design and MHT of magnetic dot; (B) Images of Rat glioma C6 cells dual-stained with acridine orange (green) and propidium iodide (red). Scale bar: 50 μm; (C) Cell cycle distribution (black area indicates cells in G0/G1 phase; blue area indicates S phase; red area indicates G2/M phase). (a) Cells only; (b) Cells immediately after the first cycle of magnetic hyperthermia-mediated cancer therapy (MHCT); (c) Cells 24 h post-first cycle of MHCT; (d) Cells immediately after two cycles of MHCT; (e) Cells 24 h post-two cycles of MHCT; (f) Cells exposed to 250 μg/ml magnetic dot alone for 24 h; (g) Cells immediately after the first round of MHCT with magnetic dot; (h) Cells 24 h post-first round of MHCT with magnetic dot; (i) Cells immediately after two rounds of MHCT with magnetic dot; (j) Cells 24 h post-two rounds of MHCT with magnetic dot. (Reproduced with permission from [180], Copyright 2021 Elsevier B.V.).**

magnetic properties and low biotoxicity. They can efficiently accumulate in tumors through magnetic attraction forces and rapidly elevate the temperature with the assistance of AMF, effectively eradicating tumors while minimizing thermal damage to surrounding tissues. Jordan et al. utilized amino-functionalized superparamagnetic nanoparticles encapsulated in amino silane for a single intratumoral injection in Fischer rats with RG2 glioma models, followed by the application of AMF. Compared with the control group, this approach resulted in a 4.5-fold extension in animal survival [169]. Morales et al. designed a manganese-doped ferrite nanoparticle with high saturation magnetization and sustained superparamagnetic behavior, in which the cRGD peptide was modified to aggregate the nanoparticles in glioma tissue for MHT [177]. The authors demonstrated glioma cell membrane rupture, expression of heat shock protein 70, and production of ROS resulting from increased intracellular temperature under exposure to AMF ($f = 96$ kHz, $H = 47$ kA/m), providing evidence for the feasibility of spatio-temporally controllable magnetic hyperthermia for GBM therapy. Only through optimum cooperation of nanoparticle magnetic properties, ideal internalization conditions within the cells, and application situation of AMF can maximum cell killing efficiency be achieved [178,179]. Sharma et al. introduced a carboxymethyl-stevioside-modified magnetic dot as a potent agent for magnetic hyperthermia in glioma therapy. Carboxymethylation of stevioside improved the stability of the synthesized magnetic nanoparticles in water, ultimately leading to a significant increase in hyperthermia output (Fig. 12A) [180]. As shown in Fig. 12B and 12C, under repetitive rounds of localized AMF exposure in a spatially and temporally controllable manner, the cell cycle progression was delayed, leading to significant inhibition of GBM cell growth. The results indicated the promising potential of stevioside-modified magnetic dot for effective magnetic hyperthermia-based glioma therapy.

### 5.2. *Magnetomechanical therapy (MMT)*

Recently, mechanical force, which can selectively influence specific cell fates, including adhesion, differentiation, invasion, and death, has become the focus of considerable attention. Cheng et al. engineered a mitochondria-targeted iron oxide nanospinner that selectively accumulates in cell mitochondria for spatio-temporally controllable MMT. Under a rotating magnetic field (RMF), the designed nanospinner

**Table 1 – Summary of the characteristics of the six types of spatio-temporally controllable glioma therapy.**

| Types | Advantage | Disadvantage |
|---|---|---|
| PDT | non-invasiveness | oxygen dependence |
| | local treatment | phototoxicity and skin sensitivity |
| | spatio-temporally controllability | low tissue penetration |
| | remote control and manipulation properties | |
| PTT | non-invasiveness | low light-thermal conversion efficiency |
| | low toxicity | phototoxicity and skin sensitivity |
| | local treatment | low tissue penetration |
| | spatio-temporally controllability | heat resistance |
| | remote control and manipulation properties | |
| | oxygen independence | |
| | thermal ablation | |
| SDT | non-invasiveness | oxygen dependence |
| | high tissue penetration | rapid US wave attenuation unfocused US beams |
| | low damage to normal tissue | |
| | mechanical cavitation | |
| | spatio-temporally controllability | |
| | remote control and manipulation properties | |
| RT | unlimited depth of penetration | low radiosensitivity |
| | local treatment | oxygen dependence |
| | spatio-temporally controllability | radiation resistance |
| | remote control and manipulation properties | inevitable damage to the surrounding tissue |
| MHT | deep tissue penetration | low magneto-thermal conversion efficiency |
| | uniform heat production | heat resistance |
| | spatio-temporally controllability | limitations of magnetic field generating equipment |
| | remote control and manipulation properties | |
| | thermal ablation | |
| MMT | deep tissue penetration | absence of adequate research |
| | low intensity and low frequency | |
| | spatio-temporally controllability | |
| | remote control and manipulation properties | |

could spontaneously assemble and generate localized mechanical force, destroying mitochondrial function and causing glioma cell death [181]. Further, RGD-modified magnetic nanoparticles, combined with AMF and RMF, were demonstrated to be applicable for mechanical and thermal energy conversion therapy in glioma [182]. The nanoparticles served as transducers for the magnetic field, forming linear structures and efficiently converting magnetic field energy into mechanical or thermal energy. First, under 15 Hz RMF, the nanoparticles assembled to form linear aggregates, exerting mechanical forces on cellular organelles and producing ROS to sensitize glioma cells. Subsequently, further generation of moderate heat was achieved using 375 kHz AMF to induce damage to sensitized glioma cells. Under the influence of two magnetic fields with remote spatio-temporal controllability and exceptional tissue penetration, the nanoparticles exhibited ROS generation, mechanical and thermal stimulation within cells, and disruption of lysosomal and mitochondrial functions, offering significant potential for *in situ* glioma therapy.

## 6. Current status of spatio-temporally controllable therapy for glioma

The advantages and disadvantages of these spatio-temporally controllable therapy are summarized in Table 1. Despite their non-invasiveness and spatio-temporally controllability, monotherapies may exhibit limitations in clinical application, such as oxygen consumption associated with phototherapy, SDT, and RT. It is crucial to select the appropriate therapy for deep malignant glioma, balancing efficacy, side effects, and the characteristics of glioma.

Over the last few decades, the utility of external controllable stimuli in the tumor treatment has advanced with rapidly growing momentum. Devices used for external stimuli play a significant role in animal models and human subjects for spatio-temporally controllable therapy. In phototherapy, light from the laser is conveyed to the brain tumor site by a light transmitting fiber with a knob at the end, which spreads light uniformly in all directions. Unlike in mice, settings for transcranial laser stimulation need optimization for thicker human cranial bone. Additionally, a novel balloon-based device has been developed in recent years for use in cavitary PDT [183]. The device used in MHT primarily consists of a system that provides an AMF with a fixed frequency and variable magnetic field strength [169]. A tumor treatment field delivering low-intensity, intermediate-frequency alternating electric fields was approved by the FDA for newly diagnosed GBM in 2015 [184]. SDT is achieved through focusing on low-intensity and low-frequency US device. In RT for animals, small linear accelerators and positioning systems are commonly utilized. Utilization of RT devices is based on individual body size and the severity of conditions in RT of humans.

Currently, RT is one of the most widely used treatments for cancer in clinical oncology. The combination of TMZ, nivolumab, ipilimumab and bevacizumab with irradiation is frequently studied in clinical trials (ClinicalTrials.gov ID: NCT02829931 and NCT00660283). Several clinical trials have been disclosed using PDT as an intervention measure for cancer therapy, although the number of trails registered for treating glioma is limited. Muller and Wilson conducted the first randomized clinical trial using PDT as therapeutic modality for glioma. In this work, 43 patients underwent glioma resection followed by adjuvant PDT using Photofrin, resulting in increased mean survival time compared with the control group [185]. The potential of 5-aminolevulinic acid (Gliolan®)-PDT for recurrent GBM is currently being investigated in a randomized Phase II clinical trial (ClinicalTrials.gov ID: NCT04469699). A recently started Phase 0 clinical trial is evaluating SONALA-001 and MR-guided focused utrasound device (MRgFUS) as treatment for recurrent high-grade glioma (ClinicalTrials.gov ID: NCT04559685). Additionally, an ongoing early feasibility single arm study is employing the Tranberg® Thermal Therapy System and Tranberg® Thermoguide Workstation to assess the safety and feasibility of MRI-guided laser thermal ablation for brain lesions (ClinicalTrials.gov ID: NCT05296122). Clinical and preclinical cases have demonstrated the diversity and potential of spatio-temporally controllable treatment systems of glioma, proving their capability to offer effective treatment options for challenging brain tumors.

## 7. Perspectives and challenges

Patients with highly aggressive and invasive primary malignant glioma have a very poor prognosis despite undergoing treatments such as surgery and chemotherapy. Over the past few years, several excellent therapeutic options have emerged. In summary, we have presented various spatio-temporally controllable therapies that take advantage of easily controllable external stimuli, such as laser, US, radiation, and magnet, in the hopes of overcoming the challenges of treating glioma.

A number of complex interdisciplinary barriers that make glioma intractable to treatment need to be addressed before clinical translation can be achieved. First, the tight junctions of endothelial cells between the central nervous system and peripheral blood circulation form the BBB, creating an obstacle for various nanoparticles/molecules as therapeutic drugs to access the brain. Unlike therapies used for other tumors, theranostic approaches used for glioma need to overcome the BBB before reaching glioma tissue, which introduces stricter demands for designing spatio-temporally controllable materials with targeting specificity. Various techniques are being developed to improve BBB penetration in glioma. These techniques can be divided into two categories: passive targeting and active targeting. Passive targeting involves materials that target tumor tissues by exploiting the enhanced permeability and retention (EPR) effect, depending on the size, surface charge, shape, and other characteristics of materials, as well as the biology of the tumor itself. Active targeting, involving receptor-, transporters-, and bulk-negative charges-mediated transcytosis, uses various moieties such as receptor substrates, peptides, antibodies, aptamers, saccharides, and proteins, as well as surface modifications to facilitate delivery across the BBB [11,186]. Systems can be designed by varying ligands conjugated to receptors overexpressed on glioma or endothelial cells, such as the transferrin receptor, low-density lipoprotein receptor, ApoE receptors growth factors, biotin-binding proteins, insulin receptor, and others. To ensure efficient drug delivery into glioma tissue, designed systems must also target glioma lesions for precise intervention.

Second, it is critically significant to consider the long-term biosecurity risks of reagents, such as peripheral brain damage, intracranial retention, and potential systemic toxicity. There are many preclinical reagents that are not officially approved through the FDA, and relevant experimental studies are supposed to consider larger animals equivalent to humans as standard models to further promote clinical translation. Sufficient evidence proving the biosafety of spatio-temporally controllable stimuli in the brain should be provided. Moreover, treatment efficiency cannot be expected to improve without understanding therapeutic ontology. Thus, further investigation of glioma pathology is vital for pursuing novel therapies. Finally, spatio-temporally controllable glioma therapies combined with other therapeutic strategies, including chemotherapy, CDT and immunotherapy, provide a prospective platform for the treatment of glioma, compared with single therapy modalities. Researchers are supposed to understand how to employ one or multiple mechanisms in an integrated system to both comprehend and treat glioma. Future studies should focus on these issues to advance spatio-temporally controllable treatment systems of glioma toward clinical application.

The spatio-temporally controllable systems reviewed here have provided valuable insights and breakthroughs in glioma therapy. Since it can directly destroy glioma cells and improve the deep TME, including tumor microvessels, by the production of ROS, heat, or mechanical forces, external stimuli are capable of ameliorating acquired drug resistance and infiltration of glioma tissue through circumventing the mechanisms of traditional drug acting on glioma cells. Numerous preclinical *in vivo* and *in vitro* experiments have confirmed the feasibility of inducing apoptosis and destruction in glioma cells by controllable external stimuli, as well as achieving biosafety of normal cerebral tissue. We expect this review will encourage researchers working on spatio-temporally controllable technologies to adopt interdisciplinary approaches, combining external technical engineering with biological knowledge, to advance more accurate and effective spatio-temporally controllable therapies.

## Conflicts of interest

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

## CRediT authorship contribution statement

**Huiwen Zhang:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Wanqi Zhu:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Wei Pan:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation. **Xiuyan Wan:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation. **Na Li:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation. **Bo Tang:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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