chemosensors

MDPI

Review

Nanomaterials for Diagnosis and Treatment of Brain Cancer: Recent Updates

Mahwash Mukhtar [1], Muhammad Bilal [2], Abbas Rahdar [3,*], Mahmood Barani [4], Rabia Arshad [5], Tapan Behl [6], Ciprian Brisc [7], Florin Banica [8] and Simona Bungau [8,*]

1 Faculty of Pharmacy, Institute of Pharmaceutical Technology and Regulatory Affairs, University of Szeged, 6720 Szeged, Hungary; mukhtar.mahwash@pharm.u-szeged.hu
2 Huaiyin Institute of Technology, School of Life Science and Food Engineering, Huaian 223003, China; bilaluaf@hotmail.com
3 Department of Physics, Faculty of Science, University of Zabol, Zabol 538-98615, Iran
4 Department of Chemistry, Shahid Bahonar University of Kerman, Kerman 76169-14111, Iran; mahmoodbarani7@gmail.com
5 Department of Pharmacy, Quaid-i-Azam University, Islamabad 15320, Pakistan; rabia.arshad@bs.qau.edu.pk
6 Chitkara College of Pharmacy, Chitkara University, Punjab 140401, India; tapanbehl31@gmail.com
7 Department of Medical Disciplines, Faculty of Medicine and Pharmacy, University of Oradea, 410073 Oradea, Romania; brisciprian@gmail.com
8 Department of Pharmacy, Faculty of Medicine and Pharmacy, University of Oradea, 410028 Oradea, Romania; florinbanica1@gmail.com
* Correspondence: a.rahdar@uoz.ac.ir (A.R.); sbungau@uoradea.ro (S.B.)

Received: 18 October 2020; Accepted: 19 November 2020; Published: 20 November 2020

Abstract: Brain tumors, especially glioblastoma, remain the most aggressive form of all the cancers because of inefficient diagnosis and profiling. Nanostructures, such as metallic nanostructures, silica nano-vehicles, quantum dots, lipid nanoparticles (NPs) and polymeric NPs, with high specificity have made it possible to permeate the blood–brain barrier (BBB). NPs possess optical, magnetic and photodynamic properties that can be exploited by surface modification, bio composition, contrast agents' encapsulation and coating by tumor-derived cells. Hence, nanotechnology has brought on a revolution in the field of diagnosis and imaging of brain tumors and cancers. Recently, nanomaterials with biomimetic functions have been introduced to efficiently cross the BBB to be engulfed by deep skin tumors and cancer malignancies for imaging. The review focuses on nanotechnology-based diagnostic and imaging approaches for exploration in brain tumors and cancers. Moreover, the review also summarizes a few strategies to image glioblastoma and cancers by multimodal functional nanocomposites for more precise and accurate clinical diagnosis. Their unique physicochemical attributes, including nanoscale sizes, larger surface area, explicit structural features and ability to encapsulate diverse molecules on their surface, render nanostructured materials as excellent nano-vehicles to cross the blood–brain barrier and convey drug molecules to their target region. This review sheds light on the current progress of various kinds of nanomaterials, such as liposomes, nano-micelles, dendrimers, carbon nanotubes, carbon dots and NPs (gold, silver and zinc oxide NPs), for efficient drug delivery in the treatment and diagnosis of brain cancer.

Keywords: nanomaterials; nanoparticles; liposomes; blood–brain barrier

1. Introduction

The brain is the most vital and amazing three-pound organ protected within the skull and is responsible for regulating memory, sensitive motor functions and many other processes and is composed of the cerebrum, cerebellum and brain stem as well as four lobes (frontal, parietal,

occipital and temporal). The cerebellum is the largest part of the brain, accompanying right and left hemispheres performing higher sensory and motor functions as well as controlling movements; it is accompanied with the cerebrum, functionalized for muscle, posture and movement coordination. However, the cerebellum and cerebrum are connected to the spinal cord via the brain stem, located under the cerebrum. It performs many automatic functions. Moreover, the significant four lobes of the brain are linked with proper propagation of behavioral functions [1]. However, any malfunction in the anatomical structure of the brain and abnormal growth of cells in an uncontrolled manner leads to disruption in the normal functional capabilities of the brain [2]. According to the statistics of the National Brain Tumor Society in 2016, approximately 78,000 people are diagnosed and 16,616 people die from malignant brain tumors in the USA every year [3]. Abnormal growth of mass cells can be static and metastatic, leading to the development of benign and malignant cancers [4]. Brain tumors are associated with increased intracranial pressure, headaches, vomiting, altered consciousness and seizures. Moreover, brain tumors can be further elaborated and classified according to their growth and location in the respective brain cells [5]. The most common site for brain tumor invasion is in brain glial cells [6]. Brain glial cells can be further classified into four grades (grade 1 to grade IV) by the WHO guidelines [7]. Grades I and II are termed as low-grade tumors and grades III and IV are classified as higher-grade tumors [8]. Metastatic brain tumor development is more common in adults than children [9]. Moreover, lung cancer in males and breast cancer in females propagates towards brain tumor metastasis [10]. Etiological causes of brain cancer are still unidentified. Metastatic brain cancer (tumor) treatment requires crucial medication parameters of non-chemotherapeutics, chemotherapeutics, radiation and surgical techniques [11]. Non-chemotherapeutic drugs are preferred to relieve tumor-associated headache and epileptic seizures [12,13]. However, chemotherapeutic drugs help in mitigating tumor mass and edema as well as killing cancer cells [14]. Similarly, radiation therapy can be used to circumvent mass of brain tumors via precise, focused beams that target the tumor while sparing the surrounding brain [15–17]. A combination of four drugs (lomustine, temozolomide, procarbazine and vincristine) has been used along with radiation therapy [18]. However, combination of all treatments regarding brain cancer is exceptionally challenging, as the blood–brain barrier (BBB) offers a great barrier towards successful drug delivery into the central nervous system. Furthermore, it is difficult to target for anti-cancer drugs because of its complex anatomical structure and physiology for protection of the central nervous system (CNS). The BBB is a prime factor responsible for maintaining the flow of essential electrolytes and cells between blood and the brain, for maintaining the homeostasis of the CNS and shielding neural cells and tissues from pathogenic toxins and is selective in the uptake of certain drugs via lacking fenestrations for transport of drugs of a large size [19,20]. Regrettably, all the therapeutics designed to target brain cancer are challenging and lack targeted delivery also because of their large size [21,22]. Moreover, the complicated structure of the BBB is attributed to the special brain mitochondrial cells, efflux transporters and tight junctions and results in lowering the bioavailability of chemotherapeutic drugs and narrowing the therapeutic window [23–25].

Prognosis of brain cancer can be identified via correct diagnosis and various diagnostic tests for brain cancer, including computed axial tomography (CAT scan/CT) with or without intravenous contrast [26]. However, intraoperative magnetic resonance imaging (MRI) may also be useful during surgery to guide tissue biopsies and tumor removal [27]. Magnetic resonance spectroscopy (MRS) is used to examine the tumor's chemical profile, and positron emission tomography (PET scan) is helpful in detecting tumor recurrence [28,29]. Diagnosis of brain cancer is challenging due to the huge existence of gaps complementing over-testing, overdiagnosis, overtreatment, non-specificity and the heterogenous nature of brain cancer [30].

Nanomedicine has revolutionized the field of medical diagnostics and treatment [20,31,32] and significantly proved to improve the pharmacological and pharmacokinetic pattern of unstable anti-cancer drugs, helping them in crossing the BBB [33]. Moreover, from previous prestigious research, it is evident that nanoparticles (NPs) are the best strategy to overcome the BBB and efficiently treat brain cancer [34]. NPs have the capability to bypass the BBB as nanocarriers, without disrupting the

functionalization of the BBB [35]. Furthermore, NPs help in slow and sustained drug release directly into brain via attaching correct ligands, thus mitigating peripheral toxicities [36]. However, interestingly, the mechanistic approach of NPs in the BBB is because they efficiently open the tight junctions owing to their feasible small size and enable the anti-cancer drug to penetrate the BBB [37]. Moreover, after crossing the BBB, NPs are endocytosed by endothelial cells and release the drug inside the cell [38]. Furthermore, there are very interesting approaches to highlight the performance of NPs via conjugating them with thiolated and preactivated polymers to efficiently inhibit the P-glycoprotein (P-gp) efflux to increase the residence time of the drug [39]. Therefore, in reference to brain cancer, various types of nanomedicines, including liposomes (conventional, long-circulating, active-targeting, stimuli-sensitive and cationic liposomes), pro-drugs, dendrimers, nano-micelles, polymersomes, gold NPs, nanogels, quantum dots and magnetic NPs, were successfully synthesized and characterized for treating brain cancers via conjugating with specified receptors to cross the BBB proficiently (Figure 1) [40,41]. Nanomedicine has also been enormously involved in the detection of brain cancer with higher sensitivity, cost-effectiveness and minimized overdiagnosis and underdiagnosis of cancer [42].

Therefore, the conventional diagnostic approach has been replenished with highly stable, non-toxic self-assembled gadolinium chelates NPs. Gadolinium ions in the chelates have the capability of maximum loading to enhance the imaging effect [43]. Furthermore, gadolinium can be utilized in another way for obtaining more promising results via conjugating them with interleukins, peptides, epidermal growth factor receptors and specified antibodies to enhance the targeting capability and imaging of tumors [44]. Most novel and efficient nano-diagnoses involves the use of gadolinium metallofullerene NPs [45]. Gadolinium metallofullerene NPs have an amino group ($–NH_3^+$)-charged cage surface exhibiting excellent 1 H MR relaxivity [46]. Therefore, in brief, it is concluded that designed NPs are more suitable for understanding the regulatory mechanisms of the BBB and show promising delivery as well as diagnosis to overcome the mortality of dreadful brain cancer.

Related to all the information above and continuing the efforts of our research group regarding the synthesis of nanomaterials and investigation about their potential bio applications [47–74], in the present paper, we reviewed the most recent published papers focused on various nanomaterials applicable in the diagnosis and treatment of brain cancer. Thus, our review-type research highlights the most relevant and newest information, bringing them to the attention of all those interested in the NPs–brain cancer relationship.

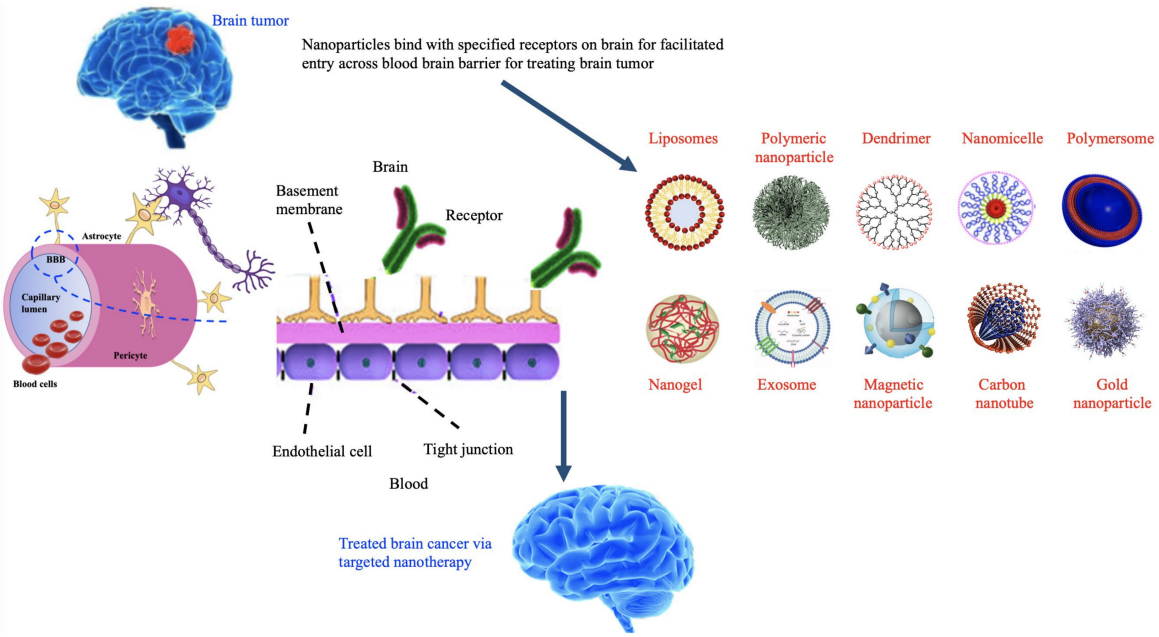

Figure 1. Brain cancer treated with novel nanoparticle (NP) therapy.

2. Nanomaterials for Treatment of Brain Cancer (Brain Tumor)

Rapid progress in nanotechnology for biological applications has a considerable impact on nanomedicine. Nanotechnology facilitates the synthesis and manipulation of materials at a nanoscale, thus assisting in developing emerging tools for the diagnosis, treatment, monitoring and control of biological systems. Nanomaterials are defined as a set of substances with any external dimension at the nanoscale or having an internal or surface structure at the nanoscale, approximately in the size range of 1–100 nm [75]. The application of nanostructured materials for drug delivery to the brain constitutes a prospective approach, as they can easily cross the BBB due to their nano-size and can transport drug molecules to their target region [76]. In relation to potential drug delivery to the brain, various nanomaterials, such as gold NPs, liposomes, dendrimers, carbon nanotubes and micelles, have been inspected. Drugs are efficiently delivered to the brain due to NPs' ability to overcome/mask the BBB's restrictive nature to drug molecules. It is of significance that therapeutic substances or drugs can be transported to the brain at substantially lower concentrations compared to the standard doses of free drugs, leading to safe drug administration to achieve therapeutic effectiveness [77]. NPs have more unique physicochemical properties than their corresponding bulk materials, such as a large surface area, high drug loading, feasibility of incorporating both hydrophilic and hydrophobic substances and high stability [78]. Besides composition, the properties of NPs depend on their shape and size. It is important to control their shape and size and minimize aggregation to obtain monodispersed NPs for internalization by cells [79,80]. Some applications of NPs are attributed to their higher surface–mass ratio than other particles, which enables them to bind, absorb or carry other molecules. Moreover, they can be functionalized or manufactured with two or more materials to enhance their physical properties [81].

2.1. Liposomes

Liposomes are spherical vesicles which consist of both biodegradable natural or synthetic phospholipid bilayers and aqueous compartments. These nanospheres are formed spontaneously because of the amphiphilic character of phospholipids [82]. They can be categorized into unilamellar vesicles (ULVs) or multilamellar vesicles (MLVs), based on the synthesis methods and post-formation processing. ULVs (one lipid bilayer, 50–250 nm) enclose a large aqueous core and are suitable to entrap hydrophilic drugs, whereas MLVs (two or more concentric lipid bilayers arranged like an onion skin, 1–5 μm) preferentially encapsulate lipid-soluble drugs. Generally, MLVs have a greater entrapped volume compared to ULVs, while unilamellar liposomes exhibit a much faster release rate than MLVs with two to three lamellar bilayers and a hydrodynamic diameter of 250 nm [83]. They can fuse with tumor cells and enter the extracellular matrix via endocytosis to release drugs [84]. Liposomes can use passive or active mechanisms for targeting the tumor. Though active tumor targeting is not inevitably more effective compared to passive targeting, it is beneficial to target micro metastases, vasculature and blood tumor [85]. Engineering and coating of liposomes with polyethylene glycol (PEG) can improve biocompatibility, water-solubility, targeted drug delivery, controlled release and half-life and reduces toxicity [86]. The surface of the liposome can also be functionalized by incorporating a large number of macromolecules, including antibodies, peptides, aptamers polymers or polysaccharides, to further improve the blood circulation duration and brain-oriented drug delivery (Figure 2). The size of liposomes has a considerable effect on their half-life in blood; smaller-size liposome nanostructures (up to 100 nm) easily penetrate tumors, whereas large-size liposomes display a shorter half-life due to their better recognition by the phagocytic system [84]. In recent years, liposomes have been widely applied as nanocarriers in the treatment of various cancers and neurological disorders.

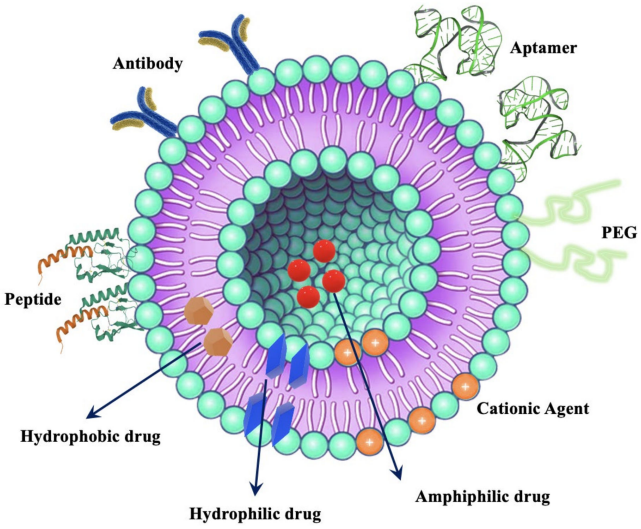

Figure 2. Schematic representation of the main liposomal drugs and targeting agents that improve liposome affinity and selectivity for brain delivery. PEG: polyethylene glycol.

Lakkadwala et al. [87] formulated and characterized a dual-functionalized liposome-based nanotherapeutic system by surface modification with transferrin (Tf) and peptide-penetratin (Pen) for receptor-mediated transcytosis and increased penetration to cell, respectively (Figure 3).

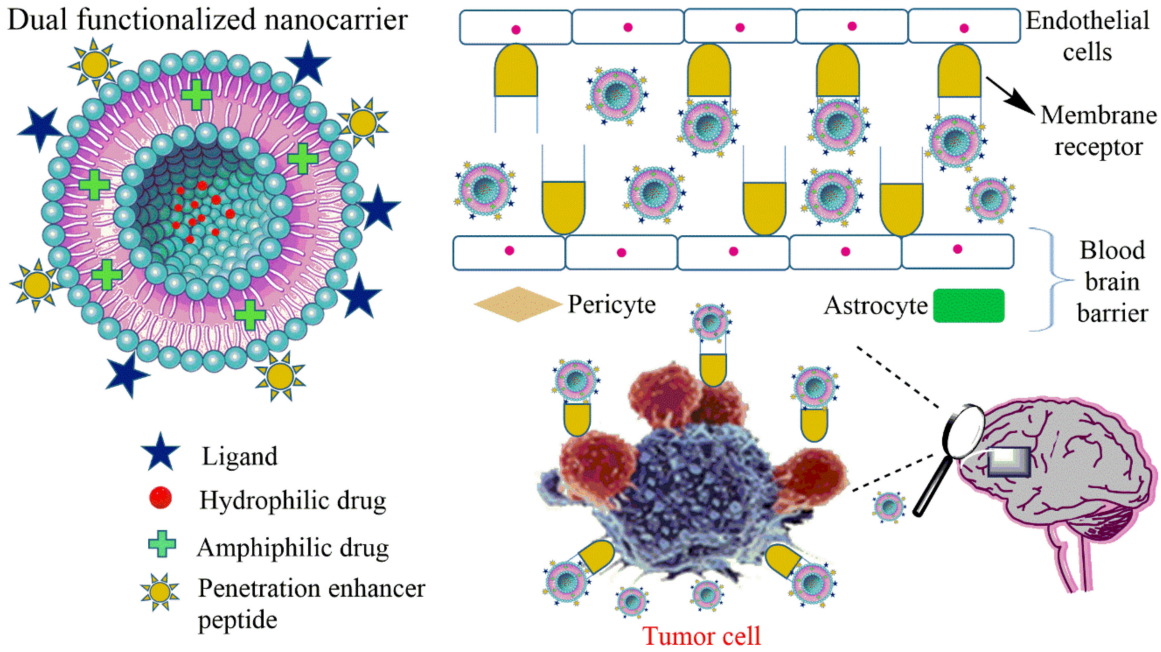

Figure 3. Schematic display of dual-functionalized nanocarrier-based therapeutic system for brain tumor.

Two chemotherapeutics (i.e., erlotinib and doxorubicin (DOX)) were then loaded into developed liposomes for enhancing their translocation to invasive glioblastoma tumor via the BBB. Co-delivery of erlotinib and doxorubicin encapsulated Tf-Pen liposomes and displayed substantially improved translocation (~15%) across the BBB, leading to tumor reversion in an in vitro brain tumor prototype. In vitro, hemocompatibility and cytotoxicity assays corroborated outstanding biocompatibility, indicating its suitability for in vivo administration. In contrast to free drugs, the Tf-Pen liposomes

loaded with erlotinib and doxorubicin showed 3.3- and ~12-fold increased accumulation in mouse brain, respectively. Furthermore, the nano-liposomal system also demonstrated improvised anti-cancer efficiency by reverting about 90% of tumor in mouse brain without any toxic effects, which showed its high impact on the therapy of individuals associated with glioblastoma.

Polyethylene glycolated (pegylated, PEGylated) vitamin E (D-α-tocopherol polyethylene glycol 1000 succinate or TPGS) has shown great potential to improve the therapeutic attributes of vitamin E and is, thus, extensively used in the drug and food industries. Muthu et al. [88] fabricated TPGS-wrapped liposomes and used them for the encapsulation of docetaxel to develop a drug delivery system for the treatment of a brain tumor. The efficacy of the synthesized nano-liposomal systems was compared with the bare and stealth liposomes (PEG-coated liposomes). A solvent injection technique was used to prepare coumarin-6- or docetaxel-loaded liposomes, then they were characterized, and their cellular uptake and cytotoxicity were assessed using C6 glioma cells. TPGS-coated liposomes exhibited a particle size in the range of 126–191 nm. After 24 h culture with C6 glioma cells, the nude, commercial Taxotere-, PEG- and TPGS-coated liposomes showed an IC50 value of 31.04, 37.04, 7.70 and 5.93 μg/mL, respectively. In comparison to PEG liposomes, the TPGS-capped nanoliposomes presented superior advantages in vitro.

Paclitaxel is a microtubule-directed antitumor drug which displays potent activities against different tumors, including lung, ovarian, brain tumor, etc. [89]. Nevertheless, the efficiency of commercially available paclitaxel preparation towards gliomas is not satisfactory due to the lack of penetration ability to the BBB [90]. Likewise, artemether also exhibits potent cytotoxicity against various kinds of cancer cells by the downregulation of expression of vascular endothelial growth factor (VEGF), hypoxia-inducible factor-1a, matrix metalloproteinase-9 and some associated proteins [91]. Previously, it has been considered a functional nanotherapeutic system to translocate drugs through the BBB, destroy vasculogenic mimicry brain channels and eradicate stem cells in the brain tissue. Using paclitaxel and artemether as the antitumor drug and apoptosis regulating agent, a new type of paclitaxel- and artemether-loaded liposomal system was prepared. The enhanced efficacy of the liposomes was associated with vasculogenic mimicry (VM) channel destruction and apoptosis induction in brain cancer cells by triggering pro-apoptotic proteins and apoptotic enzymes and impeding antiapoptotic protein factors [92].

2.2. Nano-Micelles

Micelles are an exciting class of amphiphilic spherical nanostructures which are produced by the self-aggregation of amphiphilic molecules in water above a particular critical concentration (the so-called critical micelle concentration). Micelles have both hydrophilic and hydrophobic regions. The shell of micelles is surrounded by the hydrophilic region of the molecules, while the hydrophobic region constitutes the cores, where lipophilic bioactives are entrapped [93]. These are promising nanocarriers with considerably high capacities for loading chemotherapeutics which are formulated for targeting site-specific ovarian cancer [94,95]. Micelles (with a size range of 10–100 nm) facilitate significant penetrability and endocytosis by ovarian cancer cells and reduce non-specific targeting of normal cells [96]. In contrast to other drug carriers, nano-micelles are endowed with a set of unique features, such as kinetic and thermodynamic stability, improved biocompatibility, durable plasma circulation, perforation to inflamed tissues and tumors and the capability of incorporating a large number of hydrophobic chemotherapeutics owing to their dynamic structure [93]. Amongst nanocarriers, micelles have attracted significant attention in recent years as a carrier for targeted drug delivery to treat brain cancer. Due to their nano-dimensions, they are not readily recognized and removed by the phagocytic system, and their hydrophilic shells display enhanced permeability and retention effect [97]. Agrawal et al. (2017) [98] speculated the mechanism of docetaxel-loaded bio-adhesive micelles for brain tumor therapy. Given the exceptional bio-adhesive properties, chitosan was merged with transferrin during micelle fabrication to realize the synergistic effects of adsorptive- and receptor-assisted transcytosis via chitosan and transferrin receptor, respectively. This nano-theragnostic

approach improved the transport of docetaxel-encapsulated micelles system into C6 glioma cells that substantiated the effectiveness of newly proposed bio-adhesive micelles for brain cancer therapy. The bioavailability of targeted and non-targeted nano-micelles was 4.08- and 2.89-times higher compared to pristine Docel™, respectively, after a treatment of 48 h [98].

Sonali et al. (2016) [99] formulated transferrin-encapsulated docetaxel (DTX)-loaded vitamin E TPGS micelles for the therapy of brain tumor. A solvent casting method was applied to prepare micelles without and with transferrin conjugation. Transferrin was conjugated with the TPGS-COOH carboxyl group by carbodiimide chemistry using N-hydroxy succinimide (NHS) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC) in phosphate buffer. The as-synthesized transferrin-conjugated micelles of 520 nm achieved over 80% drug encapsulation efficacy, and drug release was continued for more than 24 h with about 50% drug release. In vivo experimental results corroborated TPGS micelles as a prospective nanocarrier for brain therapy because of their enhanced solubility, permeability and targeted drug delivery, leading to prolonged and improved brain targeting of DTX than that to non-targeted micelle formulations.

In recent years, dual drug-based targeting therapeutic nanomedicines have also been developed for brain treatment. Dual-targeting theragnostic liposomes can efficiently target brain tumor and the blood–brain barrier and augment therapeutic efficiency by a synergistic effect without damaging normal cells. A dual-targeted paclitaxel plus artemether micelle system was constructed to enhance the transportation ratio via the BBB, achieving glioma cell-directed delivery and inhibition of VM formation and impeding the invasiveness of glioma cells. For this purpose, artemisia and paclitaxel were simultaneously incorporated in micelle vesicles as modulating and anti-cancer agents, respectively. The developed dual-targeted paclitaxel/artemether-based micelles exhibited excellent release profiles in the simulated body fluids and remained stable during the entire process of targeted drug delivery to glioma cells. These findings reveal the potential capability of crossing the BBB and enriching drugs inside the glioma microenvironment. The mechanistic analysis demonstrated that this dual system extensively improved the expression of caspase-3 and enhanced apoptosis of U87 cell lines to a certain level [100]. In another study, Niu et al. (2020) [101] developed a dual-targeting DOX-integrated micelle (GF-DOX) for delivering drugs through the BBB to target tumor regions in mice. The results revealed a significantly higher cellular uptake of GF-DOX to mouse brain microvascular endothelial cells (BMVECs) via clathrin- and caveolae-mediated endocytosis. Compared to the control sample, the bioavailability of DOX was profoundly increased ($p < 0.05$) in the brain using GF-DOX. Due to dual-targeting GF-DOX effects, the survival time of tumor-carrying mice was dramatically more extended than the free control group. It can be inferred that the dual targeting nanotherapeutics could enhance the efficiency of anti-cancer medications, both in vivo and in vitro, in suppressing brain tumor.

2.3. Dendrimers

Dendrimers are a class of well-ordered nanosized hyper-branched polymers. Researchers have developed a wide variety of dendrimers in the last few decades, and the design and preparation of new kinds of dendrimers is continuing [102,103]. Owing to their well-organized three-dimensional architecture and enormous surface functionalities, these hyperbranched polymers are considered as promising drug carriers. Drug molecules can be attached to the surface groups or encapsulated within the interior void of the dendrimers. Due to the presence of a vast number of functional groups on the dendrimer surface, various therapeutic molecules and drugs can be efficiently accommodated by conjugation. They present more excellent properties than other drug delivery systems, such as nanoscopic size, size consistency, large functional groups, fast cell entry, adjustable size, reduced uptake by macrophages, targeted delivery and widespread transport through biological membranes by transcytosis [104]. The biocompatibility characteristic of dendrimer polymers can be improved by surface modification, such as glycosylation, PEGylation, acetylation, and amino acid functionalization, which provides safe therapy to normal cells. To achieve targeted delivery and selectivity of brain

tumor cells, the surface of dendrimers can be decorated with targeting ligands that facilitate cancer cell reorganization without affecting the viability of normal cells [105].

Dendritic polymers, i.e., poly (amidoamine) (PAMAM) dendrimer, have gained prodigious importance as robust polymeric nanostructures for the targeted delivery gene and drugs in cancer treatment. Therefore, multiple PAMAM dendrimer-driven nano-theragnostic drug delivery systems have been constructed in recent years to exploit their applicability for brain targeting [106,107]. Liu et al. (2019) [108] fabricated a BBB-penetrating nanocarrier system using the fourth-generation PAMAM dendrimer by integrating angiopep-2 peptide followed by conjugation of another peptide directing epidermal growth factor receptor (EGFR) to augment the glioma-targeting effect after BBB penetration.

Subsequently, doxorubicin (DOX), an antitumor drug, was loaded into the internal voids by non-covalent linkages. The controllable release of incorporated drugs from the dendrimer network in response to the acidic environment of the tumor diminished the toxic effect for normal tissues and cells in vivo and in vitro. Moreover, the conjugation of peptides onto the dendrimer carriers resulted in significant improvement in BBB penetration and improved their antitumor activities after crossing the BBB. In vivo, experimental analysis revealed that the dual functionalization of dendrimer nanocarriers exceptionally enhanced their BBB permeability and the anti-glioma effects of DOX and extended the endurance of the glioma-carrying mice. In another report, the carboxyl activation technique was used to fabricate dendrimer-cationized albumin (*d*CatAlb). The synthesized *d*CatAlb polymeric complex was coated on DOX-encapsulated poly lactic-co-glycolic acid (PLGA) NP cores to constitute a new kind of DOX-based hybrid nanotherapeutic formulation (*d*CatAlb-pDNP). The newly developed *d*CatAlb-pDNP formulation presented high drug loading capacity, inimitable pH-responsive release profile, reduced hemolysis and increased toxicity in U87MG (human brain glioblastoma cell lines). Elevated caspase-3 gene levels (5.35-fold increase) in U87MG cells revealed that caspase-mediated apoptosis is the primary mechanism associated with potent antitumor activity.

The DOX nano-formulation also exhibited long-term stability, biocompatibility and pronounced trans-epithelial infiltration passage across bEnd.3 cells. Overall, the results manifest significantly improved BBB penetration and superior anti-cancer effects of *d*CatAlb-pDNP in glioblastoma cells in a safer, biocompatible and sustained manner [109]. These studies corroborate that modified dendrimers are prospective drug delivery nanocarriers that can penetrate the BBB following receptor-assisted transcytosis and reach the glioma region for targeted treatment of brain cancer. Figure 4 shows the simplest method of constructing a ligand-decorated nanoparticle for active, targeted drug delivery in glioma, cross-linked with PEG for improved bioavailability.

2.4. Carbon Nanotubes and Carbon Dots

Carbon nanotubes (CNTs) are cylindrical-shaped nanostructures that have garnered increasing attention from pharmaceutical researchers to deliver therapeutic molecules and drugs because of their special mechanical, electronic and surface properties. The reactivity of the CNT surface facilitates the attachment of guest molecules, which increase the biocompatibility of CNTs. According to the requirements, these novel nanocarriers can be functionalized with polymers, carbohydrates, peptides and organic molecules and mainly applied to cancer therapy and targeting of tumor cells [110]. Harsha et al. (2018) [111] designed and fabricated PEG-linked CNTs conjugated with mangiferin, and the resultant phytochemical-nanotube bioconjugates were examined for protein loading capacity, cytocompatibility and drug release in vitro using U-87 cell lines. At the tumor cell pH, the drug release analysis suggested a spatiotemporal pattern. A significant reduction (1.28-fold) in the IC_{50} values indicates potent antitumor activity, and the safety of the drug was confirmed by hemolytic assay. Significant apoptotic induction with negligible necrosis by exposure to nano-conjugates was established by flow cytometry analysis. In contrast to pristine mangiferin, the drug-loaded nanoconjugate revealed a four-fold increase in the drug's bioavailability, representing the capability of functionalized nanocarriers for safer and effective transportation of phyto-therapeutics to brain

tumorous cells. A cancer-specified biotin-coated multiwalled carbon nanotube (MWCNT) and a cell-penetrable peptide (namely trans-activator of transcription-polyethylenimine-biotin (known as TAT-PEI-Biotin) encapsulating oxaliplatin (OXA)) which form together TBCNT@OXA was developed for the precise therapy of orthotopic glioma by effective penetration of the BBB. The as-modified dual targeting nano-theragnostic system promoted drug transport via the BBB and substantially enhanced targeted selectivity. In comparison to Biotin CNT (BCNT)@OXA (22.6%) and CNT@OXA (9.4%), the penetrability of TBCNT@OXA (40.4%) was considerably greater, suggesting the pivotal roles of biotin moiety and trans-activating transcriptional activator in the transport of TBCNT@OXA across the BBB [112].

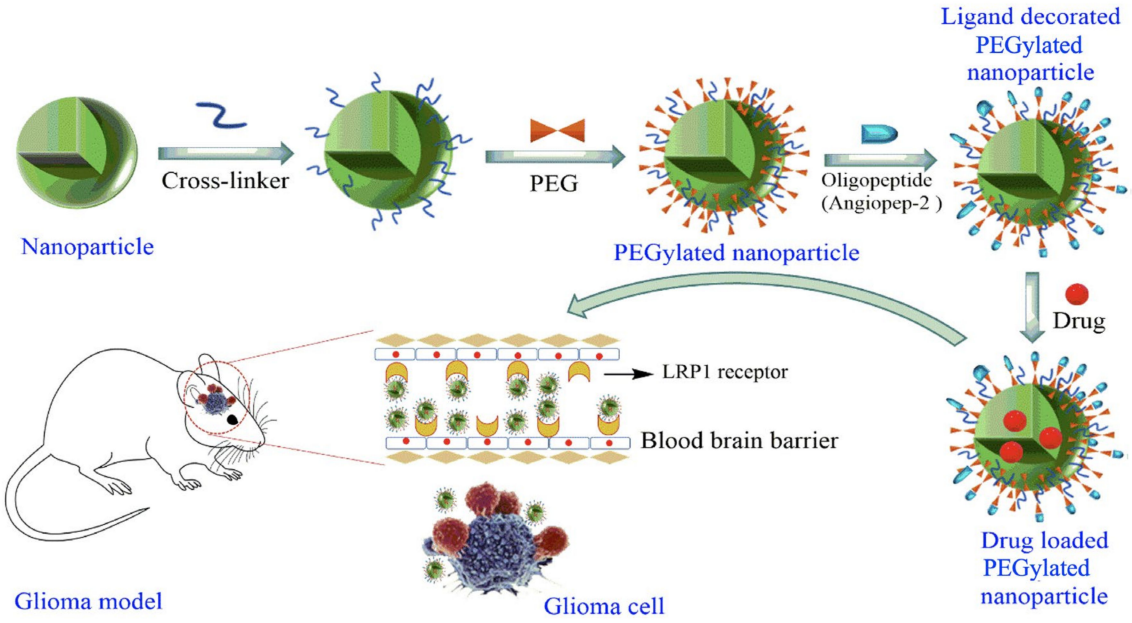

Figure 4. Diagrammatic representation of polyethylene glycolated (PEGylated) nanoparticle for improved blood circulation decorated with ligand (angio-peptide 2), an oligopeptide that has an affinity for the low-density lipoprotein receptor-related protein 1 (LRP1) receptor on brain endothelial cells, allowing targeted drug delivery across the blood–brain barrier in glioma.

Carbon dots are a new member of carbon nanostructures. These zero-dimensional nanocarriers are biocompatible, non-toxic, spherical and ultra-small particles with a size of less than 10 nm. Tremendous research focus has been directed towards these theragnostic nanoarchitectures owing to their nano size, excellent photoluminescence, good biocompatibility, multipurpose surface properties and high electron-transferring capability. These nanomaterials have emerged as a promising tool for exploitation in targeted drug delivery, biosensing, cellular imaging and many other pharmaceutical and biomedical purposes [113]. C-dots overcome the minimum observability and traceability problem of conventional drug carriers. Particularly, fluorescent carbon dots (CDs) have acquired special consideration as drug nanocarriers due to their low cytotoxicity, modified functionalities, and utmost cargo-carrying capability [114]. Zheng et al. (2014) [115] developed a novel theragnostic nanoplatform by carrying out the condensation reaction between the -COOH group of oxaliplatin and amino groups of fluorescent carbon dots. The as-fabricated system, which couples the attributes of CDs and the antitumor performance of oxaliplatin derivative, was employed for targeted drug delivery. In vitro experimental outcomes revealed that Oxa-C-dots had good biocompatibility along with potent antitumor therapeutic performance. The modified Oxa-C-dots altered the interior microenvironment of malignant cells and were internalized by the endocytosis process. Interestingly, the Oxa distribution could be traced in cancer cells due to the fluorescent properties of C-dots. Based on carbon dots, a triple-conjugated nano-drug delivery system (1.5–1.7 nm) was fabricated for glioblastoma brain

cancers by conjugating carbon dots with the targeted ligand, transferrin and two antitumor drugs, temozolomide and epirubicin [116]. The –COOH-functionalized C-dots were covalently coordinated with transferrin and drugs via an amide linkage. The therapeutic performance of this triple-conjugated nano-formulation (C-dots-trans-temo-epi) was compared with free drug preparation, C-dots-drug conjugate with no transferrin and a dual conjugated system containing encapsulation of a single drug along with transferrin glioblastoma brain cancer cell lines. Amongst the transferrin-coated formulations, C-dots-trans-temo-epi showed the highest cytotoxicity to brain tumor cells compared to single and dual conjugated nano-systems. C-DT amplified the cytotoxicity to over 85% in tumor cells, whereas the C-TT and C-ET only reduced it to 8% and 33%, respectively. Figure 5 gives an understanding of the concept of endocytosis for the aim of delivering drugs inside glioma cells by active targeting. Few such examples based on the receptor and surface chemistry modifications are mentioned in the text.

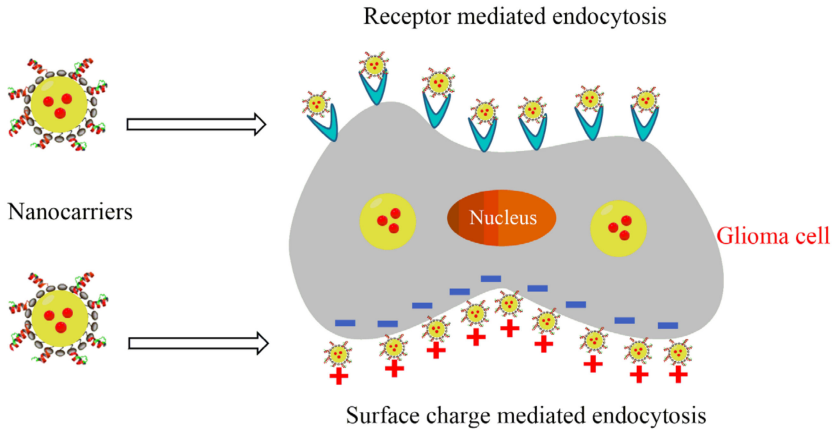

Figure 5. Schematic illustration of endocytosis by two mechanisms: receptor-mediated endocytosis and endocytosis by surface charge of nanoparticles, in glioma cells.

2.5. Gold and Silver NPs

Gold NPs (AuNPs) constitute a fascinating system with novel attributes for diverse theragnostic applications. Desirable features, such as biocompatibility, easy modification into various shapes, sizes and integration with different functional moieties, encourage researchers to focus on their applications for cancer treatment and diagnosis [117]. Like other inorganic nanostructures, AuNPs also exhibit cytotoxicity effects, which are tempted by oxidative stress. AuNPs also possess a set of advanced features, including mono dispersity, adjustable core size, easy fabrication, low toxicity, surface plasmon absorption, large surface area, binding capacity to various biomolecules and light-scattering and diagnostic properties [118]. Therapeutic molecules are loaded onto AuNPs by covalent linkages or electrostatic interactions [119]. Their size versatility is one of the most important characteristics of AuNPs, which facilitates their passage through the body circulation system. Free circulation can be used to direct AuNPs to tumor cells/surfaces [120]. Alle et al. (2020) [121] developed eco-friendly carboxymethyl xanthan gum (CMXG)-coated AuNPs (CMXG@AuNPs) using the microwave irradiation technique. Compared with traditional methods, the use of xanthan gum as a green matrix for AuNP biosynthesis offers many advantages, such as non-toxicity, cost-effectiveness, eco-friendliness and the capability to serve as an effective capping and reducing agent. The exclusive characteristics of xanthan gum led to the quick fabrication of nanosized AuNPs, which can be applied as nanocarriers in drug distribution. Doxorubicin (DOX) was loaded onto these highly crystalline and spherical NPs by electrostatic interactions. Extensive release of the loaded drug was observed in an acidic environment but was found to be insignificant at physiological pH. In contrast to free DOX, the antitumor efficacy of DOX-encapsulated CMXG@AuNPs was 4.6-fold higher. Under acidic conditions, the DOX@CMXG@AuNPs displayed profound cellular uptake compared to the free form

of DOX and exhibited excellent pH-dependent drug-releasing and anti-cancer properties. A PEGylated biogenic AuNP-based multifunctional dual nanocarrier system with the capability to deliver folate and transferrin antibody towards glioma cells was designed and fabricated. Curcin, a potent ribosomal inactivating protein was coupled with AuNPs for pH-controlled release of drugs in the acidic milieu of a tumor, thus making it friendly to healthy cells. Curcin showed pronounced therapeutic potency by restricting the proliferative and migratory properties of glioma cells. Potential toxic aspects of curcin were elucidated by mitochondrial destabilization, reactive oxygen species (ROS) production and cytoskeletal disruption. Outstanding photothermal ablation attributes of AuNPs results in the disruption of cancer colonies with high precision [122].

Silver NPs (AgNPs) display broad-spectrum biological properties based on their shape, concentration, size, route of acquaintance and biological target. Interest in the use of AgNPs has recently intensified thanks to their unique physical, chemical and biological attributes as well as their robust anti-cancer and antimicrobial activities [123]. The anti-cancer and antibacterial effects are mainly ascribed to the release of silver particles/ions in cells due to AgNP destabilization, leading to the production of ROS in massive amounts. ROS generation can exert oxidative damage to biological molecules, such as DNA, proteins and lipids, eventually resulting in cell death [124,125]. Salazar-García et al. (2020) [126] elucidated the toxic effects of AgNPs against C6 rat glioma cell lines, which were treated to varying amounts of AgNPs for a period of 24 h. Compared to the control, AgNP exposure reduced the viability of C6 rat glioma cell by 21%. A 24-h treatment with AgNPs elevated the cell populations (40%) in G0/G1 phases, but the total number of cells (60%) was decreased in G2/M stages. Multifunctional nanoplatforms composed of AgNPs and alisertib drug were formulated and connected with a 36-amino-acid-long active targeting peptide, chlorotoxin, that explicitly binds to MMP-2 receptor expressed in brain tumor cells. The therapeutic efficacy of this NP-based system was assessed against glioblastoma multiforme in vivo and in vitro. The biodistribution of NPs in healthy animal models and their influence on tumor mitigation were examined by radiolabeling with ^{99m}Tc. Results revealed a significant in vivo tumor reduction by the use of the newly developed silver/alisertib@PNPs–chlorotoxin conjugate [127].

2.6. Zinc Oxide NPs

Besides gold and silver NPs, zinc oxide NPs (ZnO-NPs) are considered inexpensive, highly interesting and attractive inorganic nanomaterials for various applications, such as in solar cells, light emission, piezoelectricity, optics, gas sensing, agriculture, cosmetics, the food industry and as anti-cancer agents [128,129]. These NPs display pronounced catalytic efficacy, biocompatibility, potent adsorption capability and fast electron-transfer kinetics [130,131]. The fabrication of different types of zinc oxide nanostructures, including nanowires, nanotubes, nanorods, nanobridges, nanobelts, nanoribbons and nano-nails, has been developed via hydrothermal synthesis, ultrasonication and thermal evaporation methods [132–134]. It has been reported that ZnO nanostructures reach the brain following oral ingestion either by neural transportation or by breaking the BBB. Shim and co-workers (2014) reported that the interaction of ZnO-NPs with brain and plasma led to induction of toxicity effects in the brain and blood. Among a range of various proteins identified on the surface of ZnO-NPs, the presence of apolipoprotein E was found to be main protein associated with the passing of NPs across the BBB to target brain disorders [135].

Reports have demonstrated that ZnO-NPs result in energy depletion and oxidative stress in microglia cells, leading to cell death [136,137]. They have shown toxic effects in the brain cancer cells of mice in contrast with the same-diameter Al_2O_3, TiO_2, CrO_3 and Fe_3O_4 counterparts [138]. Wahab et al. (2011) [139] fabricated a range of highly crystalline zinc oxide nanostructures (ZnO–MFs, ZnO–NPs, ZnO–MSs and ZnO–NSs) under various experimental conditions and assessed their antitumor efficiencies against human brain cancer (U87), normal Human Embryonic Kidney (HEK), and cervical cancer (HeLa) cell lines. Treatment of HeLa and U87 cell lines with ZnO nanostructures caused a substantial inhibition of cell growth and apoptotic death in a dose-dependent manner.

The cytotoxicity effects of ZnO-NPs were more pronounced and synergistic at elevated concentrations. Increased NP-induced cell death was also associated with a drastic increase in micronuclei formation in U87 cells that might attributed to interference with the rejoining of DNA strands by these structures. Amongst the fabricated nanostructures, nanosheets and NPs presented the most effective antitumor activities against U87 cells and HeLa cells. In a recent study, the neurotoxicity of ZnO-NPs was observed in brain tissues of mature rats by oral ingestion of 40 and 100 mg/kg for different time periods. As compared to the control, the ingestion of 40 and 100 mg/kg of ZnO-NPs for 24 h did not provoke neurotoxicity. Nevertheless, the longer exposure over seven days induced oxidative stress in brain tissues, which was evidenced by elevated malondialdehyde accompanied by a reduction in antioxidant levels. Moreover, both doses for 7 days led to DNA fragmentation and elevated levels of cytokines, caspase-3, Fas and heat shock protein-70 [140].

3. Nanomaterials for the Diagnosis and Biosensing of Brain Cancer

Nanotechnology not only improves drug delivery to diseases but also holds potential in the accurate imaging of the malignant tissues in the brain. NPs comprising biocompatible materials possess ideal physical properties, such as surface chemistry, topology, morphology, solubility, stability, etc., making them a suitable candidate to be used as image contrast structures [141]. Numerous NPs have been evaluated in the past to improve bio-distribution, accumulation in the target tissues and elimination from body. Their nano-dimension not only prolongs the circulation time but also improves the safety profile, if biocompatible nanomaterials are utilized [142]. Nanodiagnostics attenuate the signaling frequency in brain cancers and tumors as a result of phagocytosis by cells in the brain tumor due to leaky vasculature. NPs have enhanced permeation and retention in tumor-associated cells and macrophages, allowing the sharp imaging of malignant tissues, separating them from normal cells [143]. Interesting approaches are being explored to revolutionize the medical diagnosis of malignant tissues. One such technique is modulating the nanostructure's tropism by using specific coatings of peptides, bio-conjugates and nucleotides for high-precision sensing of the malignancies [144].

Some of the previously available techniques for visualization and diagnosis of the brain tumors and cancer are optical imaging, photoacoustic (PA) imaging, computed tomography (CT), positron emission tomography (PET) and fluorescence (FL) imaging techniques. Magnetic resonance (MR) imaging can be preoperative to determine the borders of the cancerous tissues and/or intraoperative to define the tumor outline during surgery by simultaneous administration of gadolinium (Gd) chelates. However, Gd has a short half-life and requires frequent administration to maintain the blood levels for effective scanning, which may not be rational. Another non-optical method is the use of intraoperative ultrasound to obtain integrated brain tissue images. However, the technique does not provide adequate information about the detection of small or superficial brain tumors. Neurophotonic technologies, such as Raman spectroscopy, optical coherence tomography, fluorescence spectroscopy and thermal imaging, are the other invasive techniques to acquire data about brain cancers and tumor tissues [145]. Altogether, cancer or tumor delineation is a complicated procedure that needs accurate preoperative imaging and sensitive, pain-free post-imaging for real-time information. Unfortunately, current imaging techniques lack accuracy, sensitivity and specificity. Over the past few years, nanotechnology has gained interest for bioimaging and biosensing (Figure 6). Nanodiagnostics uses nanotechnology in coordination with conventional diagnostic and imaging techniques [31]. The advancement in nanotechnology has made it easier to obtain data with high precision and accuracy without being invasive. One such breakthrough in this field is nanoarrays/nanochips that combine optical, magnetic and electronic properties to create small tools for diagnosis and imaging of brain cancer and tumors [146]. Moreover, multimodal/multifunctional NPs are proving potentially useful in the imaging and sensing of brain cancer and tumor. Numerous strategies have been employed to tailor NPs to work as unique imaging-guided therapeutics. Nanomaterials have been highlighted because of their biocompatibility and biodegradation characteristics. Table 1 highlights the various imaging and diagnosis technologies that are currently being explored with nanotechnology.

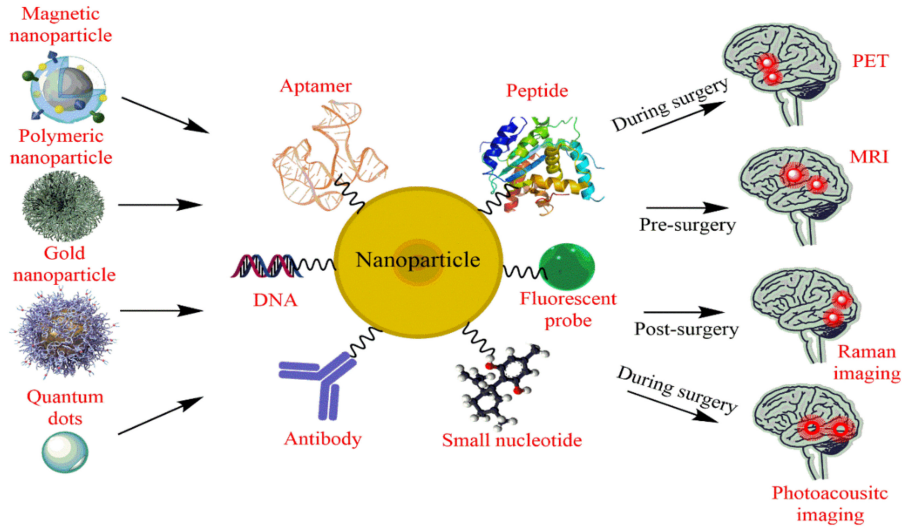

Figure 6. Nanomaterial-based imaging technology for improved diagnosis and surgery.

Table 1. Different technologies utilizing nanostructures as a platform in the diagnosis and imaging of brain cancer/tumors.

Imaging Technique	Selection Parameters Based on Characteristics	Nanostructures Used	Ref.
Surface-enhanced resonance Raman scattering imaging (SERRS)	High specificity and provides data about the location of biochemical components of cells.	SERRS NPs with ^{68}Ga comprised of gold core and silica shell	[147,148]
Magnetic resonance imaging (MRI)	Sensitive to changes in the cartilage and bone and provides an elaboration of the anatomical structure of the brain with high soft-tissue contrast.	Iron oxide NPs' surface decorated with peptides; gadolinium oxide-based NPs	[149,150]
Photoacoustic (PA) imaging	Acquires molecular data with high resolution in real-time and can be used simultaneously with other imaging techniques.	Silicon quantum sheets, molybdenum di-sulfide nanosheets conjugated with indocyanine green	[151,152]
Fluorescence (FL) imaging	Non-invasive with low spatial resolution.	Gold NPs	[153–155]
Focused ultrasound (FUS)	Real-time visualization of neural anatomy with 3D contrast-enhanced images.	Cisplatin gold NP conjugates, mesoporous organo-silica NPs	[156,157]
Multimodal imaging	Possibility to map cell density to understand heterogeneity of the tissues; high sensitivity and specificity.	SERRS-MSOT*-nanostar with gold core embedded in silica coat functionalized with PEG, SERRS-MRI gold nanoprobes	[158,159]
Positron emission tomography (PET)	Nuclear imaging technique to identify pathophysiological changes in the brain; unlimited penetration.	Alanine modified gado-fullerene NPs, self-assembled amphiphilic dendrimer nano-system	[160,161]
Computed tomography (CT)	Able to provide electron density differences among tissues to establish diagnosis.	Transferrin conjugated liposome, Lanthanide NPs	[162,163]

MSOT: multispectral optoacoustic tomography; NPs: nanoparticles.

3.1. Magnetic NPs

The exclusive properties of magnetic NPs (MNPs) make them promising imaging probes for the diagnosis of cancer. Superparamagnetic iron oxide NPs (SPIONs) and ultra-superparamagnetic iron oxide NPs (USPIONs) are a few examples of MNPs which provide unique properties, such as stability, magnetic susceptibility and physical characteristics for diagnosis and intracellular visualization of brain cancer and tumor [117]. A study reported folic acid (FA)-conjugated bovine serum albumin (BSA)-coated SPIONs for MR imaging of glioma. The biocompatibility profile and cellular uptake of FA-BSA-SPIONs demonstrated excellent results in the glioma U251 cells. Hence, nanomaterials provides a promising platform for target-specific imaging of brain cancer or tumor [164]. A similar study utilized polymeric hybrid MNPs labeled with fluorescent dye to investigate and locate human brain glioblastoma (GBM). Poly lactic-co-glycolic acid (PLGA)-modified SPIONs were labeled with polyethyleneimine (PEI)-conjugated fluorescein isothiocyanate (FITC). The labeled MNPs were endocytosed by human GBM U25 cells at a higher proportion as compared to unlabeled MNPs. The MNPs were an effective vehicle for cellular imaging and simultaneous drug delivery. Moreover, MNPs were found to be biocompatible with normal cells and posed no cytotoxicity [165].

Another interesting finding was a multifunctional nanoprobe, composed of PEGylated USPIONs conjugated with angiopep-2 to target glioblastoma tissues. Angiopep-2 has an affinity for the low-density lipoprotein receptor-related protein, which is overexpressed in glioblastoma. The biocompatibility of the nanoprobes was demonstrated to be high and the nanostructures efficiently imaged intracranial glioblastoma by crossing the BBB, which holds a promising future as a non-invasive diagnostic tool [166].

3.2. Metallic NPs

Diagnostic and therapeutic applications of gold NPs (AuNPs) were used in the past for rheumatological disorders and infections. Numerous ligands and enzymes were decorated on the surface of AuNPs for immuno-analysis and diagnosis of cancer cells. AuNPs have optical properties, such as plasmon resonance, to image the biological disorders. CT, FUS and MR imaging can easily detect AuNPs [167]. MR imaging can detect and monitor cancerous and tumorous tissues by utilizing AuNPs, as they are biocompatible and easily tunable [168].

AuNPs enhance the fluorescence in FL imaging when administered intravenously rather than with direct administration in the tumor tissues. FL imaging gives better visualization by intravenous infusion in glioma [169]. At present, biocompatible templates are being explored together with AuNPs for glioma imaging. New trends have revolutionized CT imaging with simultaneous radionuclide therapy. In one such study, chlorotoxin peptide functionalized AuNPs were synthesized and labeled with radionuclide ^{131}I. The AuNPs demonstrated an X-ray attenuation property and cytocompatibility. The developed nanoprobe was able to cross the BBB in the rat glioma model [170]. Recent studies have demonstrated the use of AuNPs because of good biocompatibility profiles in the in vivo imaging of brain tumors. Different BBB-crossing enhancers can also be attached to the surface of AuNPs. Few such ligands are transferrin, fibroblast growth factors, antibodies and low-density lipoproteins. Attachment of surface ligands improves the imaging of brain cancer or tumors at the subcellular level by multiphoton microscopy and scanning electron microscopy [171]. One study demonstrated surface decorated AuNPs for visualizing GBM at the subcellular level. A small peptide, CBP4, was attached to AuNPs to target CD133 on the tumor cells. Peptide-coated AuNPs exhibited biocompatibility when localized in cytosol, assessed with stimulus-responsive fluorescence [172].

Another sensitive imaging tool for accurate delineation of GBM is the silica-based iron oxide nanocomposite. Near-infrared fluorescent silica-coated NPs with iron oxide cores have high fluorescence in the intraoperative imaging of GBM. Such silica NPs can visualize tumor-associated macrophages in both in vitro and in vivo FL imaging. These NPs have the advantage of being water-dispersible and functioning as multimodal contrast agents [173]. Fluorescent silica NPs coated with glucose and glucose-poly (ethylene glycol) methyl ether amine (Glu-PEG) were designed and

tested for their ability to penetrate the BBB. Confocal laser scanning microscopy imaging revealed that the NPs reached the brain tissue, making them as new potentials for BBB penetration for diagnosis [174]. The other efficient cancer theragnostic for glioma was synthesized as a near-infrared nanoprobe. The nanoprobes incorporated organoplatinum (II) metallocycles and the Food and Drug Administration (FDA) approved polymer, Pluronic F127. The novel nanoprobe was photostable and demonstrated real-time monitoring in cancer therapeutics. The nano-system was efficiently internalized in U87MG cells as compared to no internalization in non-cancerous cells [175].

3.3. Quantum Dots

Quantum dots (QDs) are an alluring platform for the imaging of cancers/tumors because of their tunable properties and flexibility to be used with fluorescent characteristics, with large Stokes shifts and narrow emission bands for high-resolution images. Besides, they can be used as dual-modality images for mapping abnormalities in the brain during surgery [176]. Figure 7 demonstrates the salient properties of QDs for better imaging and the mechanism of interaction with the surface receptors of the cell membrane.

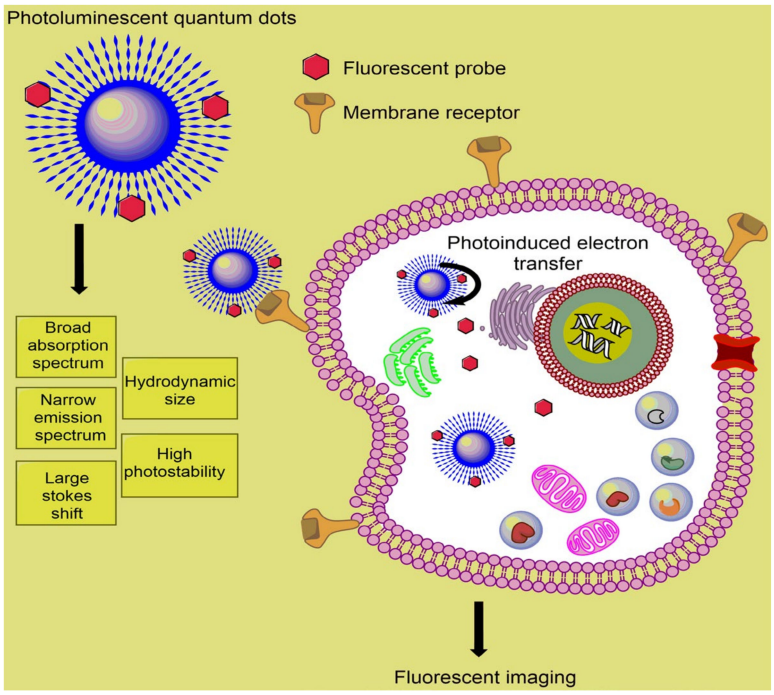

Figure 7. Interaction of quantum dots (QDs) with the membrane receptors and the mechanism of generation of florescence inside the cell for imaging.

PEG-coated QDs based on CdSe/ZnS were explored as novel nanoprobes for glioma imaging. Asparagines-glycine-arginine peptides (NGR) targeting CD13 glycoprotein on tumor cells were integrated into these QDs. These NGR-PEG-QDs were able to target CD13 on glioma tissues and contributed to fluorescence in an in vivo evaluation, which might help in the surgical resection of glioma [177]. Another interesting study explained the use of a hybrid nanomaterial-based imaging probe for glioma. A lipid phase nanobubble was designed and comprised of non-toxic indium phosphide QDs. The nanoprobe highlighted better in vivo and in-situ diagnostic potential devoid of cytotoxicity. Nanobubbles were activated by ultrasound and accumulated in the brain tumor tissues and demonstrated dual characteristics of being imaged by optical and ultrasound imaging techniques [178]. Lately, fluorescence-guided surgery is an emerging field for tumor resection. Based on this concept, a QD-labeled aptamer (QD-Apt) was designed to bind specifically to the surface of the tumor. The A32 aptamer was chosen because of its ability to bind the epidermal growth factor receptor

variant III (EGFRvIII), located on the surface of glioma cells. The QD-Apt nanoprobes were non-toxic and imaged tumor tissues in mice bearing EGFRvIII by crossing the BBB [179]. Cadmium-based QDs modified with PEG were investigated for glioma imaging. The QDs were linked with interleukin-13 (IL-13) to enhance their uptake by the glioma stem cells by targeting the 1L13Rα2 surface receptor. Transmission electron microscopy confirmed the uptake of QDs. Moreover, the IL-linked QDs were more distinct than the non-targeted glioma tumors as indicated by flow cytometry. Such QDs may serve as a diagnostic platform for the prognosis of glioma [180]. In another interesting study, novel green fluorescent polysaccharide QDs nano-bioconjugates were developed. The nanostructures of carboxymethylcellulose were functionalized with L-cysteine and poly-L-arginine. Confocal microscopy was performed to investigate the cellular uptake of the nanohybrids. These non-toxic nanoconjugates were very promising for bioimaging in brain cancer [181].

Recently, graphene QDs have gained popularity in the imaging of glioblastoma because of their low cytotoxicity as compared to other QDs. The tunable conductivity of graphene QDs makes them ideal for biosensing. Moreover, the chirality and shape of graphene impart characteristics to the graphene QDs that determine their absorption and photoluminescence. Besides, the sp^2 hybridized fraction in the graphene QDs plays an important role in their photoluminescence, which can be controlled by the appropriate mixing of sp^2 hybridized fractions of elements along with other components [182]. Enhanced photoluminescence is possible due to gamma irradiation of graphene. Irradiated graphene QDs yield more florescence than non-irradiated graphene structures. Gamma irradiation of graphene QDs is being explored for the photodynamic therapy of the GBM. The methodology works by the localization of oxygen molecules in the cell and photosensitizers, which later convert oxygen to reactive singlet oxygen to cause photo cytotoxicity. A study demonstrated the high photoluminescence and quantum yield of graphene-based QDs to allow imaging of cancer [183]. Another study reported that gamma irradiation of 50 kGy significantly improves bioimaging with sharp imaging capacity in cancer tissues. The UV illumination of the graphene QDs not only generates singlet oxygen but also yields high florescence for the simultaneous therapy and imaging of cancerous tissues [184]. Presently, novel two-dimensional inorganic compounds, MXenes, are being studied in conjugation with QDs. The potential of MXene-based QDs for the photothermal therapy and imaging in the glioma cells is being exploited. The advancement in the QDs theragnostic have made the image guided therapy possible in both the NIR-I and NIR-II bio windows. Altogether, QDs are biodegradable, tunable and biocompatible for in vivo imaging of glioma [185].

3.4. Polymeric Nano Vehicles

Commercially available contrast-enhanced MR imaging in tumor resection is disappointing in different aspects, such as short circulation time, poor BBB penetration and toxicity. Polymers have always been in demand for their biodegradation and biocompatibility profiles. Polymers are being utilized to improve MR imaging in gliomas, designed on the concept of nanotechnology. One recent study explored the potential of red fluorescent carbonized polymer dots with high internalization in glioma cells along with low toxicity, high photostability and long emission/excitation wavelengths. Such nanoprobes help in real-time image-guided surgery efficiently [186]. Similarly, biocompatible and photostable polymeric NPs decorated with cyclo (Arg-Gly-Asp-D-Phe-Lys (mpa)), to actively target integrin on the tumor cells, were designed, with an ability to absorb near-infrared beams for precise PA imaging and spatiotemporal photothermal therapy. The polymeric NPs pictured glioma at 3-mm depth with a high signal to noise ratio. Hence, polymeric NPs were found to be promising in glioma cell imaging by the PA technique [187]. Semiconducting polymers were developed by the fluorination strategy to yield fluorescence in the precise diagnosis of brain tumor. The bright near-infrared-designed polymer dots yielded three-fold enhanced images compared to non-fluorinated counterparts [188]. False-positive and ambiguous images remain the problem with existing imaging techniques. Hence, a robust strategy was exploited to design a polymeric nanostructure attached to an image contrast agent with an intrinsic T_1/T_2 dual-mode characteristic. Nanostructure coordination

polymers demonstrated low toxicity, high stability and dual T_1/T_2 contrast ability in the murine glioblastoma model when linked to paramagnetic iron moiety. Furthermore, the bio distribution of the polymeric contrast nanostructure was persistent and gave sharp images with dial mode [189].

3.5. Multimodal Imaging with Nanomaterials

At present, multimodal imaging is being explored for a more accurate and promising diagnostic application for imaging brain gliomas. As it is easy to link the diagnostic and therapeutic characteristics together at one platform, nanomaterials offer this property in a very precise way [190]. Dual or multimodal imaging has recently emerged as an effective technique that builds on the concept of active targeting by the use of ligands/markers/aptamers to make imaging sensitive to targeted tissues. Furthermore, external physical targeting modalities, such as PA and MR imaging, may also be incorporated in these diverse multimodal techniques [191].

A theragnostic liposome vehicle was designed that integrated QDs and SPIONs along with cilengitide, a peptide that inhibits angiogenesis in tumor cells, for targeting brain glioma tissue using magnetic guidance. X-ray photon spectroscopy revealed the encapsulation of SPIONs and QDs in liposomes successfully. Cellular uptake of the multimodal nano-vehicles was enhanced under magnetic targeting, which aided in accurate resection of glioma by surgery [192]. In another study, the influence of nanomaterials on the imaging of brain tumors was studied. Near-infrared molecules were encapsulated in the nanostructures together with USPIONs for simultaneous multimodal imaging and photothermal therapy. Nanostructures enhanced fluorescence imaging by PA imaging and magnetic resonance imaging signal by MR imaging. The novel photothermal therapy hybrid contrast nanostructure optimized multimodal imaging in mouse models [193]. Similarly, a dynamic study highlighted the advantage of fluoro-magnetic systems as an emerging diagnostic vehicle for brain cancer. Nanotubes having fluoro-magnetic properties were synthesized as multimodal probes. Self-assembled pH-sensitive nanotubes permitted enhanced magnetic resonance. pH-sensitive chromophore made it easier to map the acidic spatial distribution during the imaging. The multimodal nanocomposites crossed the BBB in animal studies, demonstrating the effective imaging of brain cancer by MR and FL imaging [194]. Peptide-modified SPIONs were synthesized and used to image the GBM using dual-modality, MR and sensitive optical imaging. PEPHC1 peptide was attached to SPIONs to target EGFRvIII in GBM. Nanostructures were found to be biodegradable, non-toxic and tunable for tumor imaging [195]. The boundary between normal cells and glioma cells is very difficult to differentiate precisely. Therefore, a combination of dual imaging can diagnose the tumor margin efficiently. A biomimetic catalase-integrated albumin nanoprobe was designed to amplify phototherapy and imaging. The photo-theragnostic nanoprobe enabled FL and PA imaging together with infrared thermal imaging, which made the differentiation between normal and tumor cells possible [196].

3.6. Extracellular Vesicles (EVs) and Exosomes

Gliomas remain a malignant brain tumor and need reliable and sensitive non-invasive prognosis and diagnosis. Extracellular vesicles (EVs) carry molecular components from their parental cells. EVs are membrane-coated NPs which are released from few cells of the body and are composed of DNA, RNA, lipids and proteins. Additionally, EVs tend to breach the BBB through transcytosis [197]. EVs can be found in the serum of glioma patients and express EGFR protein as an expression of glioma. So, EGFR in EVs can be detected to have an accurate diagnosis of the malignancy of the tumor [198]. Therefore, EV-based diagnostic tools for brain tumors are being explored. Biomimetic nanostructures with EV lipid envelopes might be an effective theragnostic tool for uptake into the tumor cells that need to be still exploited [199].

Similarly, exosomes are well defined nano-size lipid bilayer extracellular vesicles shed by almost all types of cells. These exosomes express coding and non-coding RNAs and lipids that can be used as a non-toxic strong cargo loaded diagnostic tool to cross the BBB [200]. A study focused on SPIONs loaded into glioma-targeted exosomes for imaging. Neuropilin-1-targeted peptide was grafted on

exosomes' membrane. Moreover, the exosomes were loaded with curcumin for their theragnostic property as well. The SPIONs were mediated by magnetic flow and accumulated in the tumor tissues for simultaneous imaging and therapeutic functions [201].

3.7. Mesenchymal Stem Cells Engineered Nano-Based Imaging

Recently, mesenchymal stem cell (MSC) therapy has been a novel exploration in the diagnosis of brain tumors and cancers [202,203]. Various administration routes, including intraventricular, intrathecal, intravenous and intralesional, are being exploited for imaging and diagnosis of brain tissue deformities. However, the administration of contrast agents via carotid arteries is beneficial because of low off-site accumulation, thereby reducing toxicity. Hence, contrast agents can be delivered to the brain efficiently. MSC-based therapies utilize MR and PA imaging to produce signals for quantitative measurements of tumors, most popularly GBM [204].

One study by Yang Qiao et al. demonstrated the use of MSCs with multifunctional SPIOs with gold (SPIO@Au) with a combined ability to be detected by both MR and PA imaging. MSCs labeled with SPIO@Au and unlabeled MSCs were compared in terms of their ability to be imaged using MR and PA imaging after being injected via the internal carotid artery. SPIO@Au MSCs were localized in the tumor, did not exhibit cell differentiation or toxicity and continued payload even after 72 h of injection as compared to unlabeled MSCs [205].

In another study, the intraparenchymal route of administration was exploited. Bicyclo (6.10.0) nonyne (BCN)-conjugated glycol chitosan NPs were designed. These BCN NPs were then loaded with oleic acid-coated SPIOs along with near-infrared fluorescent dye. Later, they were labeled with human MSCs that increased imaging sensitivity in a mouse model and were found to have high labeling efficiencies in vitro and in vivo [206]. Similarly, a stem cell-mediated nanogel was designed and labeled with ultra-small iron oxide NPs for MR imaging of brain tumor. The prepared nanogel enhanced the tumor site accumulation after intravenous injection with significantly enhanced MR signal and strength as compared to the nanogel free of stem cells. The stem cell-based nanogel was a safe, biocompatible and promising vehicle for enhanced MR imaging of tumors [207]. Another robust surveillance was performed of an MSC-based nanocomposite that was developed for glioblastoma. The study was based on the fabrication of long persistent luminescence nanoparticles (LPLNP-PPT-TRAIL). PPT refers to polyetherimide, PEG and trans-activator of transcription, whereas TRAIL is the human tumor necrosis factor-related apoptosis-induced ligand for targeting glioblastoma. Near-infrared luminescence efficiently tracked the tumor tropic migration of engineered MSCs in glioblastoma, making the nano-vehicle a novel target diagnostic tool [208]. MSCs have BBB-infiltrating properties and advancements are taking place for further promising cellular imaging as target vectors. In an interesting finding, placenta-derived MSCs (P-MSCs) were used to monitor the localization of nano-vehicles in glioblastoma stem-like cells. PEG-coated SPIOs were synthesized and labeled with MSCs to improve trafficking in the glioblastoma after intravenous administration. The nanostructures were detected in a mouse model of glioblastoma by MR imaging, making nano-vectors a state-of-the-art theragnostic technique for real-time cellular imaging [209].

3.8. Biomimetic Nanocomposites

Pathophysiological changes hinder paracellular transport across the blood–brain barrier in tumor cells in GBM, which have been infiltrated in normal tissues. In the past, many approaches have been used to diagnose the deeper tumor tissues but none proved promising in the long run [47]. Internalization of nanomaterials into complex tumor microenvironments can be achieved by attaching the surface molecules sensitive to the neo-vasculature of GBM. Furthermore, homotopic targeting by using cancer cell membrane coating is a recent advancement to envision brain tumor cells. The navigation and targeting of tumor by crossing the BBB through biological surface-engineered nanocomposites are, hence, possible. Therefore, the cell membrane can be used as a "tactical shell" to target tumors by multifunctional nanocomposites in cores to achieve multimodal imaging.

A study based on this hypothesis was conducted recently, in which bio-orthogonally labeled brain tumor cell membrane coated nanocomposites were developed to diagnose GBM. Additionally, cRGD, an endothelial integrin receptor-targeting peptide, was attached to the surface of biomimetic nanocomposites to achieve active targeting of tumors. The cRGD-labeled biomimetic contrast NPs localized in tumor tissue and presented real-time guided resection. Cells derived from tumor cells were used as the coat enabled BBB penetration for optimized targeting through multimodal imaging [210]. Owing to good BBB permeation by biomimetic materials, a novel nanocarrier was designed to target glioblastoma. The brain metastatic tumor cell membrane was coated on the nanocarriers and decorated with indocyanine green to facilitate tumor cell imaging and phototherapy. The biomimetic NPs demonstrated good permeation across the BBB and were found to be non-toxic [211]. Similarly, biomimetic proteolipid NPs grafted with indocyanine green were constructed to allow imaging of glioma. The nanostructures allowed glioma cell imaging, tumor cell detection and excellent phototherapy. The NPs were able to permeate across the BBB and glioma cell margins were visualized by near-infrared FL imaging with no significant cytotoxicity [212,213]. Bovine serum albumin fluoride-linked nanocrystals were designed by a simple biomimetic technique and provided complementary T_1-T_2 imaging in glioma. The biomimetic nanocrystals had a better imaging property than non-biomimetic structures. The T_1 property facilitated high resolution between the tissues and T_2 modality facilitated the detection of tumors [214].

4. Conclusions

Tumors and cancer of the brain display a complex pathophysiology that is impossible to be observed with conventional imaging technologies. However, the advent of nanotechnology has made it possible to image brain tissues with high resolution and sensitivity by actively targeting the tumor cells. Various NPs have been designed and engineered to penetrate the BBB to perform diagnostic and imaging roles. Nanomaterials have been very promising because of their flexible properties, biocompatibility, safety and biodegradation. The use of nanoparticle probes for in vivo imaging and molecular profiling is a potential prospect in this era with novel discoveries. However, with the latest developments, safety concerns must be addressed before clinical implications. This review delineates the current progress of various kinds of nanomaterials, such as liposomes, nano-micelles, dendrimers, carbon nanotubes, carbon dots and NPs (gold, silver and zinc oxide NPs), for efficient drug delivery in the treatment of brain cancer. The application of nanostructured materials for the delivery of drugs to the brain constitutes a prospective approach, as they can easily cross the BBB due to their nano-size and can transport drug molecules to their target region. It is of significance that therapeutic substances or drugs can be transported to the brain at substantially lower concentrations compared to the standard doses of the free drugs, leading to safe drug administration to achieve therapeutic effectiveness. Nevertheless, special properties, such as biodegradability, biocompatibility, water solubility, durable shelf life and prolonged circulating half-life, should be well characterized before using nanomaterials in medicine. Furthermore, the assessment of toxicity concerns of nanocarriers for clinical application is of supreme importance and must be deliberated carefully.

Author Contributions: All authors have equally contributed to this paper and agreed with the final form of the submitted manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Zhang, J. Secrets of the Brain: An introduction to the brain anatomical structure and biological function. *arXiv* **2019**, arXiv:1906.03314.
2. Schiavi, S.; Ocampo-Pineda, M.; Barakovic, M.; Petit, L.; Descoteaux, M.; Thiran, J.-P.; Daducci, A. A new method for accurate in vivo mapping of human brain connections using microstructural and anatomical information. *Sci. Adv.* **2020**, *6*, eaba8245. [CrossRef] [PubMed]
3. Stiller, C.A.; Gatta, G. *Oxford Textbook of Cancer in Children*; Oxford University Press: Oxford, UK, 2020.
4. Wang, X.; Yu, Y.; Zang, L.; Zhang, P.; Ma, J.; Chen, D. Targeting clusterin induces apoptosis, reduces growth ability and invasion and mediates sensitivity to chemotherapy in human osteosarcoma cells. *Curr. Pharm. Biotechnol.* **2020**, *21*, 131–139. [CrossRef] [PubMed]
5. Zumel-Marne, A.; Kundi, M.; Castaño-Vinyals, G.; Alguacil, J.; Petridou, E.T.; Georgakis, M.K.; Morales-Suárez-Varela, M.; Sadetzki, S.; Piro, S.; Nagrani, R. Clinical presentation of young people (10–24 years old) with brain tumors: Results from the international MOBI-Kids study. *J. Neuro-Oncol.* **2020**, *147*, 427–440. [CrossRef]
6. Bhaduri, A.; Di Lullo, E.; Jung, D.; Müller, S.; Crouch, E.E.; Espinosa, C.S.; Ozawa, T.; Alvarado, B.; Spatazza, J.; Cadwell, C.R. Outer radial glia-like cancer stem cells contribute to heterogeneity of glioblastoma. *Cell Stem Cell* **2020**, *26*, 48–63.e46. [CrossRef] [PubMed]
7. Brat, D.J.; Aldape, K.; Colman, H.; Holland, E.C.; Louis, D.N.; Jenkins, R.B.; Kleinschmidt-DeMasters, B.; Perry, A.; Reifenberger, G.; Stupp, R. cIMPACT-NOW update 3: Recommended diagnostic criteria for "Diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV". *Acta Neuropathol.* **2018**, *136*, 805–810. [CrossRef]
8. Nakamura, K.; Smyth, M.J. Myeloid immunosuppression and immune checkpoints in the tumor microenvironment. *Cell. Mol. Immunol.* **2020**, *17*, 1–12. [CrossRef]
9. Nicolaides, T.; Nazemi, K.J.; Crawford, J.; Kilburn, L.; Minturn, J.; Gajjar, A.; Gauvain, K.; Leary, S.; Dhall, G.; Aboian, M. Phase I study of vemurafenib in children with recurrent or progressive BRAFV600E mutant brain tumors: Pacific Pediatric Neuro-Oncology Consortium study (PNOC-002). *Oncotarget* **2020**, *11*, 1942. [CrossRef]
10. Stewart, C.A.; Gay, C.M.; Xi, Y.; Sivajothi, S.; Sivakamasundari, V.; Fujimoto, J.; Bolisetty, M.; Hartsfield, P.M.; Balasubramaniyan, V.; Chalishazar, M.D. Single-cell analyses reveal increased intratumoral heterogeneity after the onset of therapy resistance in small-cell lung cancer. *Nat. Cancer* **2020**, *1*, 423–436. [CrossRef]
11. Arvanitis, C.D.; Ferraro, G.B.; Jain, R.K. The blood–brain barrier and blood–tumour barrier in brain tumours and metastases. *Nat. Rev. Cancer* **2020**, *20*, 26–41. [CrossRef] [PubMed]
12. Wojcicki, A.V.; Kadapakkam, M.; Frymoyer, A.; Lacayo, N.; Chae, H.-D.; Sakamoto, K.M. Repurposing drugs for acute myeloid leukemia: A worthy Cause or a Futile Pursuit? *Cancers* **2020**, *12*, 441. [CrossRef] [PubMed]
13. Blake, Z.; Marks, D.K.; Gartrell, R.D.; Hart, T.; Horton, P.; Cheng, S.K.; Taback, B.; Horst, B.A.; Saenger, Y.M. Complete intracranial response to talimogene laherparepvec (T-Vec), pembrolizumab and whole brain radiotherapy in a patient with melanoma brain metastases refractory to dual checkpoint-inhibition. *J. Immunother. Cancer* **2018**, *6*, 25. [CrossRef] [PubMed]
14. Li, X.; Lovell, J.F.; Yoon, J.; Chen, X. Clinical development and potential of photothermal and photodynamic therapies for cancer. *Nat. Rev. Clin. Oncol.* **2020**, *17*, 657–674. [CrossRef] [PubMed]
15. Jain, K.K. A critical overview of targeted therapies for glioblastoma. *Front. Oncol.* **2018**, *8*, 419. [CrossRef] [PubMed]
16. El Demerdash, N.; Kedda, J.; Ram, N.; Brem, H.; Tyler, B. Novel therapeutics for brain tumors: Current practice and future prospects. *Expert Opin. Drug Deliv.* **2020**, *17*, 9–21. [CrossRef]
17. Puttemans, J.; Lahoutte, T.; D'Huyvetter, M.; Devoogdt, N. Beyond the Barrier: Targeted Radionuclide Therapy in Brain Tumors and Metastases. *Pharmaceutics* **2019**, *11*, 376. [CrossRef]
18. Yan, W.; Khan, M.K.; Wu, X.; Simone, C.B. Spatially fractionated radiation therapy: History, present and the future. *Clin. Transl. Radiat. Oncol.* **2020**, *20*, 30. [CrossRef]
19. Jena, L.; McErlean, E.; McCarthy, H. Delivery across the blood-brain barrier: Nanomedicine for glioblastoma multiforme. *Drug Deliv. Transl. Res.* **2020**, *10*, 304–318. [CrossRef]
20. Zhou, Y.; Peng, Z.; Seven, E.S.; Leblanc, R.M. Crossing the blood-brain barrier with nanoparticles. *J. Control. Release* **2018**, *270*, 290–303. [CrossRef]

21. Rosenblum, D.; Joshi, N.; Tao, W.; Karp, J.M.; Peer, D. Progress and challenges towards targeted delivery of cancer therapeutics. *Nat. Commun.* **2018**, *9*, 1410. [CrossRef]
22. Shi, D.; Mi, G.; Shen, Y.; Webster, T.J. Glioma-targeted dual functionalized thermosensitive Ferri-liposomes for drug delivery through an in vitro blood–brain barrier. *Nanoscale* **2019**, *11*, 15057–15071. [CrossRef] [PubMed]
23. Ma, F.; Zhang, X.; Yin, K.-J. Micrornas in central nervous system diseases: A prospective role in regulating blood-brain barrier integrity. *Exp. Neurol.* **2020**, *323*, 113094. [CrossRef]
24. Alamu, O.; Rado, M.; Ekpo, O.; Fisher, D. Differential Sensitivity of Two Endothelial Cell Lines to Hydrogen Peroxide Toxicity: Relevance for In Vitro Studies of the Blood–Brain Barrier. *Cells* **2020**, *9*, 403. [CrossRef] [PubMed]
25. Ding, S.; Khan, A.I.; Cai, X.; Song, Y.; Lyu, Z.; Du, D.; Dutta, P.; Lin, Y. Overcoming blood–brain barrier transport: Advances in nanoparticle-based drug delivery strategies. *Mater. Today* **2020**, *37*, 112–125. [CrossRef] [PubMed]
26. Tandel, G.S.; Biswas, M.; Kakde, O.G.; Tiwari, A.; Suri, H.S.; Turk, M.; Laird, J.R.; Asare, C.K.; Ankrah, A.A.; Khanna, N. A review on a deep learning perspective in brain cancer classification. *Cancers* **2019**, *11*, 111. [CrossRef]
27. Molina, E.S.; Schipmann, S.; Stummer, W. Maximizing safe resections: The roles of 5-aminolevulinic acid and intraoperative MR imaging in glioma surgery—Review of the literature. *Neurosurg. Rev.* **2019**, *42*, 197–208. [CrossRef]
28. Choi, I.Y.; Andronesi, O.C.; Barker, P.; Bogner, W.; Edden, R.A.; Kaiser, L.G.; Lee, P.; Marjańska, M.; Terpstra, M.; de Graaf, R.A. Spectral editing in 1H magnetic resonance spectroscopy: Experts' consensus recommendations. *NMR Biomed.* **2020**, e4411. [CrossRef]
29. Sharma, U.; Jagannathan, N.R. Metabolism of prostate cancer by magnetic resonance spectroscopy (MRS). *Biophys. Rev.* **2020**, *12*, 1163–1173. [CrossRef]
30. Atun, R.; Bhakta, N.; Denburg, A.; Frazier, A.L.; Friedrich, P.; Gupta, S.; Lam, C.G.; Ward, Z.J.; Yeh, J.M.; Allemani, C. Sustainable care for children with cancer: A Lancet Oncology Commission. *Lancet Oncol.* **2020**, *21*, e185–e224. [CrossRef]
31. Zottel, A.; Videtič Paska, A.; Jovčevska, I. Nanotechnology meets oncology: Nanomaterials in brain cancer research, diagnosis and therapy. *Materials* **2019**, *12*, 1588. [CrossRef]
32. Zhang, Y.; Li, M.; Gao, X.; Chen, Y.; Liu, T. Nanotechnology in cancer diagnosis: Progress, challenges and opportunities. *J. Hematol. Oncol.* **2019**, *12*, 137. [CrossRef] [PubMed]
33. Martins, J.P.; das Neves, J.; de la Fuente, M.; Celia, C.; Florindo, H.; Günday-Türeli, N.; Popat, A.; Santos, J.L.; Sousa, F.; Schmid, R. The solid progress of nanomedicine. *Drug Deliv. Transl. Res.* **2020**, *10*, 726–729. [CrossRef] [PubMed]
34. Mendiratta, S.; Hussein, M.; Nasser, H.A.; Ali, A.A.A. Multidisciplinary role of mesoporous silica nanoparticles in brain regeneration and cancers: From crossing the blood–brain barrier to treatment. *Part. Part. Syst. Charact.* **2019**, *36*, 1900195. [CrossRef]
35. Neves, A.R.; Queiroz, J.F.; Lima, S.A.C.; Reis, S. Apo E-functionalization of solid lipid nanoparticles enhances brain drug delivery: Uptake mechanism and transport pathways. *Bioconjug. Chem.* **2017**, *28*, 995–1004. [CrossRef] [PubMed]
36. Muthuraman, A.; Rishitha, N.; Mehdi, S. Role of nanoparticles in bioimaging, diagnosis and treatment of cancer disorder. In *Design of Nanostructures for Theranostics Applications*; Elsevier: Amsterdam, The Netherlands, 2018; pp. 529–562.
37. Nowak, M.; Helgeson, M.E.; Mitragotri, S. Delivery of nanoparticles and macromolecules across the blood–brain barrier. *Adv. Ther.* **2020**, *3*, 1900073. [CrossRef]
38. Gonzalez-Carter, D.; Liu, X.; Tockary, T.A.; Dirisala, A.; Toh, K.; Anraku, Y.; Kataoka, K. Targeting nanoparticles to the brain by exploiting the blood–brain barrier impermeability to selectively label the brain endothelium. *Proc. Natl. Acad. Sci. USA* **2020**, *117*, 19141–19150. [CrossRef]
39. Lopalco, A.; Denora, N. Nanoformulations for Drug delivery: Safety, toxicity, and efficacy. In *Computational Toxicology*; Springer: Berlin/Heidelberg, Germany, 2018; pp. 347–365.
40. El-Sawy, H.S.; Al-Abd, A.M.; Ahmed, T.A.; El-Say, K.M.; Torchilin, V.P. Stimuli-responsive nano-architecture drug-delivery systems to solid tumor micromilieu: Past, present, and future perspectives. *ACS Nano* **2018**, *12*, 10636–10664. [CrossRef]

41. Lombardo, D.; Kiselev, M.A.; Caccamo, M.T. Smart nanoparticles for drug delivery application: Development of versatile nanocarrier platforms in biotechnology and nanomedicine. *J. Nanomater.* **2019**, *2019*, 3702518. [CrossRef]
42. Biswas, A.; Shukla, A.; Maiti, P. Biomaterials for interfacing cell imaging and drug delivery: An overview. *Langmuir* **2019**, *35*, 12285–12305. [CrossRef]
43. Wu, X.; Yang, H.; Yang, W.; Chen, X.; Gao, J.; Gong, X.; Wang, H.; Duan, Y.; Wei, D.; Chang, J. Nanoparticle-based diagnostic and therapeutic systems for brain tumors. *J. Mater. Chem. B* **2019**, *7*, 4734–4750. [CrossRef]
44. Andrade, K.N.; Pérez, A.M.P.; Arízaga, G.G.C. Passive and active targeting strategies in hybrid layered double hydroxides nanoparticles for tumor bioimaging and therapy. *Appl. Clay Sci.* **2019**, *181*, 105214. [CrossRef]
45. Wang, S.; Zhou, Z.; Yu, G.; Lu, N.; Liu, Y.; Dai, Y.; Fu, X.; Wang, J.; Chen, X. Gadolinium metallofullerene-polypyrrole nanoparticles for activatable dual-modal imaging-guided photothermal therapy. *ACS Appl. Mater. Interfaces* **2018**, *10*, 28382–28389. [CrossRef] [PubMed]
46. Zeng, Y.; Li, H.; Li, Z.; Luo, Q.; Zhu, H.; Gu, Z.; Zhang, H.; Gong, Q.; Luo, K. Engineered gadolinium-based nanomaterials as cancer imaging agents. *Appl. Mater. Today* **2020**, *20*, 100686. [CrossRef]
47. Barani, M.; Mirzaei, M.; Torkzadeh-Mahani, M.; Adeli-sardou, M. Evaluation of Carum-loaded Niosomes on Breast Cancer Cells: Physicochemical Properties, In Vitro Cytotoxicity, Flow Cytometric, DNA Fragmentation and Cell Migration Assay. *Sci. Rep.* **2019**, *9*, 7139. [CrossRef] [PubMed]
48. Barani, M.; Mirzaei, M.; Torkzadeh-Mahani, M.; Lohrasbi-Nejad, A.; Nematollahi, M.H. A new formulation of hydrophobin-coated niosome as a drug carrier to cancer cells. *Mater. Sci. Eng. C* **2020**, *113*, 110975. [CrossRef] [PubMed]
49. Barani, M.; Mirzaei, M.; Torkzadeh-Mahani, M.; Nematollahi, M.H. Lawsone-loaded Niosome and its antitumor activity in MCF-7 breast Cancer cell line: A Nano-herbal treatment for Cancer. *DARU J. Pharm. Sci.* **2018**, *26*, 11–17. [CrossRef]
50. Barani, M.; Nematollahi, M.H.; Zaboli, M.; Mirzaei, M.; Torkzadeh-Mahani, M.; Pardakhty, A.; Karam, G.A. In silico and in vitro study of magnetic niosomes for gene delivery: The effect of ergosterol and cholesterol. *Mater. Sci. Eng. C* **2019**, *94*, 234–246. [CrossRef]
51. Barani, M.; Sabir, F.; Rahdar, A.; Arshad, R.; Z Kyzas, G. Nanotreatment and Nanodiagnosis of Prostate Cancer: Recent Updates. *Nanomaterials* **2020**, *10*, 1696. [CrossRef]
52. Barani, M.; Torkzadeh-Mahani, M.; Mirzaei, M.; Nematollahi, M.H. Comprehensive Evaluation of Gene Expression in Negative and Positive Trigger-based Targeting Niosomes in HEK-293 Cell Line. *Iran. J. Pharm. Res.* **2020**, *19*, 166–180.
53. Bilal, M.; Barani, M.; Sabir, F.; Rahdar, A.; Kyzas, G.Z. Nanomaterials for the treatment and diagnosis of Alzheimer's disease: An overview. *NanoImpact* **2020**, *20*, 100251. [CrossRef]
54. Das, S.S.; Bharadwaj, P.; Bilal, M.; Barani, M.; Rahdar, A.; Taboada, P.; Bungau, S.; Kyzas, G.Z. Stimuli-Responsive Polymeric Nanocarriers for Drug Delivery, Imaging, and Theragnosis. *Polymers* **2020**, *12*, 1397. [CrossRef] [PubMed]
55. Davarpanah, F.; Yazdi, A.K.; Barani, M.; Mirzaei, M.; Torkzadeh-Mahani, M. Magnetic delivery of antitumor carboplatin by using PEGylated-Niosomes. *DARU J. Pharm. Sci.* **2018**, *26*, 57–64. [CrossRef] [PubMed]
56. Ebrahimi, A.K.; Barani, M.; Sheikhshoaie, I. Fabrication of a new superparamagnetic metal-organic framework with core-shell nanocomposite structures: Characterization, biocompatibility, and drug release study. *Mater. Sci. Eng. C* **2018**, *92*, 349–355. [CrossRef] [PubMed]
57. Hajizadeh, M.R.; Maleki, H.; Barani, M.; Fahmidehkar, M.A.; Mahmoodi, M.; Torkzadeh-Mahani, M. In vitro cytotoxicity assay of D-limonene niosomes: An efficient nano-carrier for enhancing solubility of plant-extracted agents. *Res. Pharm. Sci.* **2019**, *14*, 448.
58. Hajizadeh, M.R.; Parvaz, N.; Barani, M.; Khoshdel, A.; Fahmidehkar, M.A.; Mahmoodi, M.; Torkzadeh-Mahani, M. Diosgenin-loaded niosome as an effective phytochemical nanocarrier: Physicochemical characterization, loading efficiency, and cytotoxicity assay. *DARU J. Pharm. Sci.* **2019**, *27*, 329–339. [CrossRef]
59. Rahdar, A.; Hajinezhad, M.R.; Nasri, S.; Beyzaei, H.; Barani, M.; Trant, J.F. The synthesis of methotrexate-loaded F127 microemulsions and their in vivo toxicity in a rat model. *J. Mol. Liq.* **2020**, *313*, 113449. [CrossRef]

60. Rahdar, A.; Taboada, P.; Hajinezhad, M.R.; Barani, M.; Beyzaei, H. Effect of tocopherol on the properties of Pluronic F127 microemulsions: Physico-chemical characterization and in vivo toxicity. *J. Mol. Liq.* **2019**, *277*, 624–630. [CrossRef]
61. Torkzadeh-Mahani, M.; Zaboli, M.; Barani, M.; Torkzadeh-Mahani, M. A combined theoretical and experimental study to improve the thermal stability of recombinant D-lactate dehydrogenase immobilized on a novel superparamagnetic Fe3O4NPs@ metal–organic framework. *Appl. Organomet. Chem.* **2020**, *34*, e5581. [CrossRef]
62. Rahdar, A.; Aliahmad, M.; Samani, M.; HeidariMajd, M.; Susan, M.A.B.H. Synthesis and characterization of highly efficacious Fe-doped ceria nanoparticles for cytotoxic and antifungal activity. *Ceram. Int.* **2019**, *45*, 7950–7955. [CrossRef]
63. Rahdar, A.; Hajinezhad, M.R.; Sankar, V.S.; Askari, F.; Noura, M.; Kyzas, G.Z. Synthesis, characterization, and intraperitoneal biochemical studies of zinc oxide nanoparticles in Rattus norvegicus. *Appl. Phys. A* **2020**, *126*, 347. [CrossRef]
64. Taimoory, S.M.; Rahdar, A.; Aliahmad, M.; Sadeghfar, F.; Hajinezhad, M.R.; Jahantigh, M.; Shahbazi, P.; Trant, J.F. The synthesis and characterization of a magnetite nanoparticle with potent antibacterial activity and low mammalian toxicity. *J. Mol. Liq.* **2018**, *265*, 96–104. [CrossRef]
65. Nikazar, S.; Sivasankarapillai, V.S.; Rahdar, A.; Gasmi, S.; Anumol, P.; Shanavas, M.S. Revisiting the cytotoxicity of quantum dots: An in-depth overview. *Biophys. Rev.* **2020**, *12*, 703–718. [CrossRef] [PubMed]
66. Pillai, A.M.; Sivasankarapillai, V.S.; Rahdar, A.; Joseph, J.; Sadeghfar, F.; Rajesh, K.; Kyzas, G.Z. Green synthesis and characterization of zinc oxide nanoparticles with antibacterial and antifungal activity. *J. Mol. Struct.* **2020**, *1211*, 128107. [CrossRef]
67. Rahdar, A.; Hajinezhad, M.R.; Bilal, M.; Askari, F.; Kyzas, G.Z. Behavioral effects of zinc oxide nanoparticles on the brain of rats. *Inorg. Chem. Commun.* **2020**, *119*, 108131. [CrossRef]
68. Rahdar, A.; Hajinezhad, M.R.; Hamishekar, H.; Ghamkhari, A.; Kyzas, G.Z. Copolymer/graphene oxide nanocomposites as potential anticancer agents. *Polym. Bull.* **2020**, 1–22. [CrossRef]
69. Saravani, R.; Sargazi, S.; Saravani, R.; Rabbani, M.; Rahdar, A.; Taboada, P. Newly crocin-coated magnetite nanoparticles induce apoptosis and decrease VEGF expression in breast carcinoma cells. *J. Drug Deliv. Sci. Technol.* **2020**, *60*, 101987. [CrossRef]
70. Sivasankarapillai, V.S.; Somakumar, A.K.; Joseph, J.; Nikazar, S.; Rahdar, A.; Kyzas, G.Z. Cancer theranostic applications of MXene nanomaterials: Recent updates. *Nano-Struct. Nano-Objects* **2020**, *22*, 100457. [CrossRef]
71. Sivasankarapillai, V.S.; Pillai, A.M.; Rahdar, A.; Sobha, A.P.; Das, S.S.; Mitropoulos, A.C.; Mokarrar, M.H.; Kyzas, G.Z. On Facing the SARS-CoV-2 (COVID-19) with Combination of Nanomaterials and Medicine: Possible Strategies and First Challenges. *Nanomaterials* **2020**, *10*, 852. [CrossRef]
72. Sayadi, K.; Rahdar, A.; Hajinezhad, M.R.; Nikazar, S.; Susan, M.A.B.H. Atorvastatin-loaded SBA-16 nanostructures: Synthesis, physical characterization, and biochemical alterations in hyperlipidemic rats. *J. Mol. Struct.* **2020**, *1202*, 127296. [CrossRef]
73. Rahdar, A.; Beyzaei, H.; Askari, F.; Kyzas, G.Z. Gum-based cerium oxide nanoparticles for antimicrobial assay. *Appl. Phys. A* **2020**, *126*, 324. [CrossRef]
74. Davarpanah, A.M.; Rahdar, A.; Dastnae, M.A.; Zeybek, O.; Beyzaei, H. (1−x) $BaFe_{12}O_{19}$/x$CoFe_2O_4$ hard/soft magnetic nanocomposites: Synthesis, physical characterization, and antibacterial activities study. *J. Mol. Struct.* **2019**, *1175*, 445–449. [CrossRef]
75. Sengul, A.B.; Asmatulu, E. Toxicity of metal and metal oxide nanoparticles: A review. *Environ. Chem. Lett.* **2020**, *18*, 1659–1683. [CrossRef]
76. Quader, S.; Kataoka, K. Nanomaterial-enabled cancer therapy. *Mol. Ther.* **2017**, *25*, 1501–1513. [CrossRef] [PubMed]
77. Jain, K. Nanobiotechnology-based drug delivery to the central nervous system. *Neurodegener. Dis.* **2007**, *4*, 287–291. [CrossRef]
78. Teleanu, D.M.; Chircov, C.; Grumezescu, A.M.; Volceanov, A.; Teleanu, R.I. Impact of nanoparticles on brain health: An up to date overview. *J. Clin. Med.* **2018**, *7*, 490. [CrossRef]
79. Yasui, T.; Kaji, N.; Baba, Y. Nanobiodevices for biomolecule analysis and imaging. *Annu. Rev. Anal. Chem.* **2013**, *6*, 83–96. [CrossRef] [PubMed]

80. Frank, D.; Tyagi, C.; Tomar, L.; Choonara, Y.E.; du Toit, L.C.; Kumar, P.; Penny, C.; Pillay, V. Overview of the role of nanotechnological innovations in the detection and treatment of solid tumors. *Int J Nanomed.* **2014**, *9*, 589–613. [CrossRef]
81. Gatoo, M.A.; Naseem, S.; Arfat, M.Y.; Dar, A.M.; Qasim, K.; Zubair, S. Physicochemical properties of nanomaterials: Implication in associated toxic manifestations. *BioMed Res. Int.* **2014**, *2014*, 498420. [CrossRef]
82. Malam, Y.; Loizidou, M.; Seifalian, A.M. Liposomes and nanoparticles: Nanosized vehicles for drug delivery in cancer. *Trends Pharmacol. Sci.* **2009**, *30*, 592–599. [CrossRef] [PubMed]
83. Torchilin, V.P. Recent advances with liposomes as pharmaceutical carriers. *Nat. Rev. Drug Discov.* **2005**, *4*, 145–160. [CrossRef]
84. Bozzuto, G.; Molinari, A. Liposomes as nanomedical devices. *Int. J. Nanomed.* **2015**, *10*, 975. [CrossRef]
85. Allen, T.M.; Cullis, P.R. Liposomal drug delivery systems: From concept to clinical applications. *Adv. Drug Deliv. Rev.* **2013**, *65*, 36–48. [CrossRef]
86. Immordino, M.L.; Dosio, F.; Cattel, L. Stealth liposomes: Review of the basic science, rationale, and clinical applications, existing and potential. *Int. J. Nanomed.* **2006**, *1*, 297.
87. Lakkadwala, S.; dos Santos Rodrigues, B.; Sun, C.; Singh, J. Dual functionalized liposomes for efficient co-delivery of anti-cancer chemotherapeutics for the treatment of glioblastoma. *J. Control. Release* **2019**, *307*, 247–260. [CrossRef] [PubMed]
88. Muthu, M.S.; Kulkarni, S.A.; Xiong, J.; Feng, S.-S. Vitamin E TPGS coated liposomes enhanced cellular uptake and cytotoxicity of docetaxel in brain cancer cells. *Int. J. Pharm.* **2011**, *421*, 332–340. [CrossRef] [PubMed]
89. Zhan, C.; Gu, B.; Xie, C.; Li, J.; Liu, Y.; Lu, W. Cyclic RGD conjugated poly (ethylene glycol)-co-poly (lactic acid) micelle enhances paclitaxel anti-glioblastoma effect. *J. Control. Release* **2010**, *143*, 136–142. [CrossRef] [PubMed]
90. Postma, T.; Heimans, J.; Luykx, S.; Van Groeningen, C.; Beenen, L.; Hoekstra, O.; Taphoorn, M.; Zonnenberg, B.; Klein, M.; Vermorken, J. A phase II study of paclitaxel in chemonaive patients with recurrent high-grade glioma. *Ann. Oncol.* **2000**, *11*, 409–413. [CrossRef] [PubMed]
91. Anfosso, L.; Efferth, T.; Albini, A.; Pfeffer, U. Microarray expression profiles of angiogenesis-related genes predict tumor cell response to artemisinins. *Pharm. J.* **2006**, *6*, 269–278. [CrossRef] [PubMed]
92. Qiao, Y.; Wan, J.; Zhou, L.; Ma, W.; Yang, Y.; Luo, W.; Yu, Z.; Wang, H. Stimuli-responsive nanotherapeutics for precision drug delivery and cancer therapy. *Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol.* **2019**, *11*, e1527. [CrossRef]
93. Pantshwa, J.M.; Kondiah, P.P.; Choonara, Y.E.; Marimuthu, T.; Pillay, V. Nanodrug Delivery Systems for the Treatment of Ovarian Cancer. *Cancers* **2020**, *12*, 213. [CrossRef]
94. Yu, F.; Jiang, F.; Tang, X.; Wang, B. N-octyl-N-arginine-chitosan micelles for gambogic acid intravenous delivery: Characterization, cell uptake, pharmacokinetics, and biodistribution. *Drug Dev. Ind. Pharm.* **2018**, *44*, 615–623. [CrossRef] [PubMed]
95. Fathi, M.; Majidi, S.; Zangabad, P.S.; Barar, J.; Erfan-Niya, H.; Omidi, Y. Chitosan-based multifunctional nanomedicines and theranostics for targeted therapy of cancer. *Med. Res. Rev.* **2018**, *38*, 2110–2136. [CrossRef] [PubMed]
96. Feng, S.-T.; Li, J.; Luo, Y.; Yin, T.; Cai, H.; Wang, Y.; Dong, Z.; Shuai, X.; Li, Z.-P. pH-sensitive nanomicelles for controlled and efficient drug delivery to human colorectal carcinoma LoVo cells. *PLoS ONE* **2014**, *9*, e100732. [CrossRef] [PubMed]
97. Kim, S.; Shi, Y.; Kim, J.Y.; Park, K.; Cheng, J.-X. Overcoming the barriers in micellar drug delivery: Loading efficiency, in vivo stability, and micelle–cell interaction. *Expert Opin. Drug Deliv.* **2010**, *7*, 49–62. [CrossRef]
98. Agrawal, P.; Singh, R.P.; Sharma, G.; Mehata, A.K.; Singh, S.; Rajesh, C.V.; Pandey, B.L.; Koch, B.; Muthu, M.S. Bioadhesive micelles of d-α-tocopherol polyethylene glycol succinate 1000: Synergism of chitosan and transferrin in targeted drug delivery. *Colloids Surf. B Biointerfaces* **2017**, *152*, 277–288. [CrossRef]
99. Sonali; Agrawal, P.; Singh, R.P.; Rajesh, C.V.; Singh, S.; Vijayakumar, M.R.; Pandey, B.L.; Muthu, M.S. Transferrin receptor-targeted vitamin E TPGS micelles for brain cancer therapy: Preparation, characterization and brain distribution in rats. *Drug Deliv.* **2016**, *23*, 1788–1798. [CrossRef]
100. Mittal, S.; Ashhar, M.U.; Qizilbash, F.F.; Qamar, Z.; Narang, J.K.; Kumar, S.; Ali, J.; Baboota, S. Ligand Conjugated Targeted Nanotherapeutics for Treatment of Neurological Disorders. *Curr. Pharm. Des.* **2020**, *26*, 2291–2305. [CrossRef]

101. Niu, J.; Wang, L.; Yuan, M.; Zhang, J.; Chen, H.; Zhang, Y. Dual-targeting nanocarrier based on glucose and folic acid functionalized pluronic P105 polymeric micelles for enhanced brain distribution. *J. Drug Deliv. Sci. Technol.* **2020**, *57*, 101343. [CrossRef]
102. Nanjwade, B.K.; Bechra, H.M.; Derkar, G.K.; Manvi, F.; Nanjwade, V.K. Dendrimers: Emerging polymers for drug-delivery systems. *Eur. J. Pharm. Sci.* **2009**, *38*, 185–196. [CrossRef]
103. Noriega-Luna, B.; Godínez, L.A.; Rodríguez, F.J.; Rodríguez, A.; Zaldívar-Lelo de Larrea, G.; Sosa-Ferreyra, C.; Mercado-Curiel, R.; Manríquez, J.; Bustos, E. Applications of dendrimers in drug delivery agents, diagnosis, therapy, and detection. *J. Nanomater.* **2014**, *2014*, 507273. [CrossRef]
104. Mishra, V.; Kesharwani, P. Dendrimer technologies for brain tumor. *Drug Discov. Today* **2016**, *21*, 766–778. [CrossRef]
105. Ambekar, R.S.; Choudhary, M.; Kandasubramanian, B. Recent advances in dendrimer-based nanoplatform for cancer treatment: A review. *Eur. Polym. J.* **2020**, *126*, 109546. [CrossRef]
106. He, H.; Li, Y.; Jia, X.-R.; Du, J.; Ying, X.; Lu, W.-L.; Lou, J.-N.; Wei, Y. PEGylated Poly (amidoamine) dendrimer-based dual-targeting carrier for treating brain tumors. *Biomaterials* **2011**, *32*, 478–487. [CrossRef] [PubMed]
107. Yan, H.; Wang, L.; Wang, J.; Weng, X.; Lei, H.; Wang, X.; Jiang, L.; Zhu, J.; Lu, W.; Wei, X. Two-order targeted brain tumor imaging by using an optical/paramagnetic nanoprobe across the blood brain barrier. *Acs Nano* **2012**, *6*, 410–420. [CrossRef] [PubMed]
108. Liu, C.; Zhao, Z.; Gao, H.; Rostami, I.; You, Q.; Jia, X.; Wang, C.; Zhu, L.; Yang, Y. Enhanced blood-brain-barrier penetrability and tumor-targeting efficiency by peptide-functionalized poly (amidoamine) dendrimer for the therapy of gliomas. *Nanotheranostics* **2019**, *3*, 311. [CrossRef] [PubMed]
109. Muniswamy, V.J.; Raval, N.; Gondaliya, P.; Tambe, V.; Kalia, K.; Tekade, R.K. 'Dendrimer-Cationized-Albumin'encrusted polymeric nanoparticle improves BBB penetration and anticancer activity of doxorubicin. *Int. J. Pharm.* **2019**, *555*, 77–99. [CrossRef]
110. Mahajan, S.; Patharkar, A.; Kuche, K.; Maheshwari, R.; Deb, P.K.; Kalia, K.; Tekade, R.K. Functionalized carbon nanotubes as emerging delivery system for the treatment of cancer. *Int. J. Pharm.* **2018**, *548*, 540–558. [CrossRef]
111. Harsha, P.; Thotakura, N.; Kumar, M.; Sharma, S.; Mittal, A.; Khurana, R.K.; Singh, B.; Negi, P.; Raza, K. A novel PEGylated carbon nanotube conjugated mangiferin: An explorative nanomedicine for brain cancer cells. *J. Drug Deliv. Sci. Technol.* **2019**, *53*, 101186. [CrossRef]
112. You, Y.; Wang, N.; He, L.; Shi, C.; Zhang, D.; Liu, Y.; Luo, L.; Chen, T. Designing dual-functionalized carbon nanotubes with high blood–brain-barrier permeability for precise orthotopic glioma therapy. *Dalton Trans.* **2019**, *48*, 1569–1573. [CrossRef]
113. Mishra, V.; Patil, A.; Thakur, S.; Kesharwani, P. Carbon dots: Emerging theranostic nanoarchitectures. *Drug Discov. Today* **2018**, *23*, 1219–1232. [CrossRef]
114. Zuo, J.; Jiang, T.; Zhao, X.; Xiong, X.; Xiao, S.; Zhu, Z. Preparation and application of fluorescent carbon dots. *J. Nanomater.* **2015**. [CrossRef]
115. Zheng, M.; Liu, S.; Li, J.; Qu, D.; Zhao, H.; Guan, X.; Hu, X.; Xie, Z.; Jing, X.; Sun, Z. Integrating oxaliplatin with highly luminescent carbon dots: An unprecedented theranostic agent for personalized medicine. *Adv. Mater.* **2014**, *26*, 3554–3560. [CrossRef] [PubMed]
116. Hettiarachchi, S.D.; Graham, R.M.; Mintz, K.J.; Zhou, Y.; Vanni, S.; Peng, Z.; Leblanc, R.M. Triple conjugated carbon dots as a nano-drug delivery model for glioblastoma brain tumors. *Nanoscale* **2019**, *11*, 6192–6205. [CrossRef]
117. Sonali, M.K.V.; Singh, R.P.; Agrawal, P.; Mehata, A.K.; Datta Maroti Pawde, N.; Sonkar, R.; Muthu, M.S. Nanotheranostics: Emerging strategies for early diagnosis and therapy of brain cancer. *Nanotheranostics* **2018**, *2*, 70. [CrossRef]
118. Fan, Z.; Fu, P.P.; Yu, H.; Ray, P.C. Theranostic nanomedicine for cancer detection and treatment. *J. Food Drug Anal.* **2014**, *22*, 3–17. [CrossRef] [PubMed]
119. Norden, A.D.; Drappatz, J.; Wen, P.Y. Novel anti-angiogenic therapies for malignant gliomas. *Lancet Neurol.* **2008**, *7*, 1152–1160. [CrossRef]
120. Pandey, S.; Oza, G.; Mewada, A.; Shah, R.; Thakur, M.; Sharon, M. Folic acid mediated synaphic delivery of doxorubicin using biogenic gold nanoparticles anchored to biological linkers. *J. Mater. Chem. B* **2013**, *1*, 1361–1370. [CrossRef]

121. Alle, M.; Kim, T.H.; Park, S.H.; Lee, S.-H.; Kim, J.-C. Doxorubicin-carboxymethyl xanthan gum capped gold nanoparticles: Microwave synthesis, characterization, and anti-cancer activity. *Carbohydr. Polym.* **2020**, *229*, 115511. [CrossRef]
122. Mohamed, M.S.; Veeranarayanan, S.; Poulose, A.C.; Nagaoka, Y.; Minegishi, H.; Yoshida, Y.; Maekawa, T.; Kumar, D.S. Type 1 ribotoxin-curcin conjugated biogenic gold nanoparticles for a multimodal therapeutic approach towards brain cancer. *Biochim. Biophys. Acta (BBA)—Gen. Subj.* **2014**, *1840*, 1657–1669. [CrossRef]
123. Le Ouay, B.; Stellacci, F. Antibacterial activity of silver nanoparticles: A surface science insight. *Nano Today* **2015**, *10*, 339–354. [CrossRef]
124. Abdal Dayem, A.; Hossain, M.K.; Lee, S.B.; Kim, K.; Saha, S.K.; Yang, G.-M.; Choi, H.Y.; Cho, S.-G. The role of reactive oxygen species (ROS) in the biological activities of metallic nanoparticles. *Int. J. Mol. Sci.* **2017**, *18*, 120. [CrossRef] [PubMed]
125. Ebrahimzadeh, Z.; Salehzadeh, A.; Naeemi, A.; Jalali, A. Silver nanoparticles biosynthesized by Anabaena flos-aquae enhance the apoptosis in breast cancer cell line. *Bull. Mater. Sci.* **2020**, *43*, 1–7. [CrossRef]
126. Salazar-García, S.; García-Rodrigo, J.F.; Martínez-Castañón, G.A.; Ruiz-Rodríguez, V.M.; Portales-Pérez, D.P.; Gonzalez, C. Silver nanoparticles (AgNPs) and zinc chloride ($ZnCl_2$) exposure order determines the toxicity in C6 rat glioma cells. *J. Nanopart. Res.* **2020**, *22*, 253. [CrossRef]
127. Locatelli, E.; Naddaka, M.; Uboldi, C.; Loudos, G.; Fragogeorgi, E.; Molinari, V.; Pucci, A.; Tsotakos, T.; Psimadas, D.; Ponti, J. Targeted delivery of silver nanoparticles and alisertib: In vitro and in vivo synergistic effect against glioblastoma. *Nanomedicine* **2014**, *9*, 839–849. [CrossRef]
128. Jin, T.; Sun, D.; Su, J.; Zhang, H.; Sue, H.J. Antimicrobial efficacy of zinc oxide quantum dots against Listeria monocytogenes, Salmonella enteritidis, and Escherichia coli O157:H7. *J. Food Sci.* **2009**, *74*, M46–M52. [CrossRef]
129. Rasmussen, J.W.; Martinez, E.; Louka, P.; Wingett, D.G. Zinc oxide nanoparticles for selective destruction of tumor cells and potential for drug delivery applications. *Expert Opin. Drug Deliv.* **2010**, *7*, 1063–1077. [CrossRef]
130. Jin, B.; Bae, S.; Lee, S.; Im, S. Effects of native defects on optical and electrical properties of ZnO prepared by pulsed laser deposition. *Mater. Sci. Eng. B* **2000**, *71*, 301–305. [CrossRef]
131. Wang, Z.L. Nanostructures of zinc oxide. *Mater. Today* **2004**, *7*, 26–33. [CrossRef]
132. Lao, J.; Huang, J.; Wang, D.; Ren, Z. ZnO nanobridges and nanonails. *Nano Lett.* **2003**, *3*, 235–238. [CrossRef]
133. Zhang, H.; Yang, D.; Li, D.; Ma, X.; Li, S.; Que, D. Controllable growth of ZnO microcrystals by a capping-molecule-assisted hydrothermal process. *Cryst. Growth Des.* **2005**, *5*, 547–550. [CrossRef]
134. Ostrovsky, S.; Kazimirsky, G.; Gedanken, A.; Brodie, C. Selective cytotoxic effect of ZnO nanoparticles on glioma cells. *Nano Res.* **2009**, *2*, 882–890. [CrossRef]
135. Shim, K.H.; Hulme, J.; Maeng, E.H.; Kim, M.-K.; An, S.S.A. Analysis of zinc oxide nanoparticles binding proteins in rat blood and brain homogenate. *Int. J. Nanomed.* **2014**, *9*, 217.
136. Wei, L.; Wang, J.; Chen, A.; Liu, J.; Feng, X.; Shao, L. Involvement of PINK1/parkin-mediated mitophagy in ZnO nanoparticle-induced toxicity in BV-2 cells. *Int. J. Nanomed.* **2017**, *12*, 1891. [CrossRef] [PubMed]
137. Sharma, A.K.; Singh, V.; Gera, R.; Purohit, M.P.; Ghosh, D. Zinc oxide nanoparticle induces microglial death by NADPH-oxidase-independent reactive oxygen species as well as energy depletion. *Mol. Neurobiol.* **2017**, *54*, 6273–6286. [CrossRef] [PubMed]
138. Jeng, H.A.; Swanson, J. Toxicity of metal oxide nanoparticles in mammalian cells. *J. Environ. Sci. Health Part A* **2006**, *41*, 2699–2711. [CrossRef] [PubMed]
139. Wahab, R.; Kaushik, N.K.; Verma, A.K.; Mishra, A.; Hwang, I.; Yang, Y.-B.; Shin, H.-S.; Kim, Y.-S. Fabrication and growth mechanism of ZnO nanostructures and their cytotoxic effect on human brain tumor U87, cervical cancer HeLa, and normal HEK cells. *JBIC J. Biol. Inorg. Chem.* **2011**, *16*, 431–442. [CrossRef]
140. Attia, H.; Nounou, H.; Shalaby, M. Zinc oxide nanoparticles induced oxidative DNA damage, inflammation and apoptosis in rat's brain after oral exposure. *Toxics* **2018**, *6*, 29. [CrossRef]
141. Reddy, L.H.; Couvreur, P. Nanotechnology for therapy and imaging of liver diseases. *J. Hepatol.* **2011**, *55*, 1461–1466. [CrossRef]
142. Baetke, S.C.; Lammers, T.; Kiessling, F. Applications of nanoparticles for diagnosis and therapy of cancer. *Br. J. Radiol.* **2015**, *88*, 20150207. [CrossRef]
143. Meyers, J.D.; Doane, T.; Burda, C.; Basilion, J.P. Nanoparticles for imaging and treating brain cancer. *Nanomedicine* **2012**, *8*, 123–143. [CrossRef]

144. Weissleder, R.; Nahrendorf, M.; Pittet, M.J. Imaging macrophages with nanoparticles. *Nat. Mater.* **2014**, *13*, 125–138. [CrossRef] [PubMed]
145. Vasefi, F.; MacKinnon, N.; Farkas, D.L.; Kateb, B. Review of the potential of optical technologies for cancer diagnosis in neurosurgery: A step toward intraoperative neurophotonics. *Neurophotonics* **2016**, *4*, 011010. [CrossRef] [PubMed]
146. Tang, W.; Fan, W.; Lau, J.; Deng, L.; Shen, Z.; Chen, X. Emerging blood–brain-barrier-crossing nanotechnology for brain cancer theranostics. *Chem. Soc. Rev.* **2019**, *48*, 2967–3014. [CrossRef] [PubMed]
147. Huang, R.; Harmsen, S.; Samii, J.M.; Karabeber, H.; Pitter, K.L.; Holland, E.C.; Kircher, M.F. High precision imaging of microscopic spread of glioblastoma with a targeted ultrasensitive SERRS molecular imaging probe. *Theranostics* **2016**, *6*, 1075. [CrossRef]
148. Nicolson, F.; Andreiuk, B.; Andreou, C.; Hsu, H.-T.; Rudder, S.; Kircher, M.F. Non-invasive in vivo imaging of cancer using surface-enhanced spatially offset Raman spectroscopy (SESORS). *Theranostics* **2019**, *9*, 5899. [CrossRef]
149. Richard, S.; Boucher, M.; Lalatonne, Y.; Mériaux, S.; Motte, L. Iron oxide nanoparticle surface decorated with cRGD peptides for magnetic resonance imaging of brain tumors. *Biochim. Biophys. Acta (BBA)—Gen. Subj.* **2017**, *1861*, 1515–1520. [CrossRef]
150. Shen, Z.; Liu, T.; Yang, Z.; Zhou, Z.; Tang, W.; Fan, W.; Liu, Y.; Mu, J.; Li, L.; Bregadze, V.I. Small-sized gadolinium oxide based nanoparticles for high-efficiency theranostics of orthotopic glioblastoma. *Biomaterials* **2020**, *235*, 119783. [CrossRef]
151. Miao, Z.; Hu, D.; Gao, D.; Fan, L.; Ma, Y.; Ma, T.; Liu, X.; Zheng, H.; Zha, Z.; Sheng, Z. Tiny 2D silicon quantum sheets: A brain photonic nanoagent for orthotopic glioma theranostics. *Sci. Bull.* **2020**. [CrossRef]
152. Liu, C.; Chen, J.; Zhu, Y.; Gong, X.; Zheng, R.; Chen, N.; Chen, D.; Yan, H.; Zhang, P.; Zheng, H. Highly sensitive MoS 2–indocyanine green hybrid for photoacoustic imaging of orthotopic brain glioma at deep site. *Nano-Micro Lett.* **2018**, *10*, 48. [CrossRef]
153. Peng, C.; Gao, X.; Xu, J.; Du, B.; Ning, X.; Tang, S.; Bachoo, R.M.; Yu, M.; Ge, W.-P.; Zheng, J. Targeting orthotopic gliomas with renal-clearable luminescent gold nanoparticles. *Nano Res.* **2017**, *10*, 1366–1376. [CrossRef]
154. Davidi, E.S.; Dreifuss, T.; Motiei, M.; Shai, E.; Bragilovski, D.; Lubimov, L.; Kindler, M.J.J.; Popovtzer, A.; Don, J.; Popovtzer, R. Cisplatin-conjugated gold nanoparticles as a theranostic agent for head and neck cancer. *Head Neck* **2018**, *40*, 70–78. [CrossRef] [PubMed]
155. Feng, Q.; Shen, Y.; Fu, Y.; Muroski, M.E.; Zhang, P.; Wang, Q.; Xu, C.; Lesniak, M.S.; Li, G.; Cheng, Y. Self-assembly of gold nanoparticles shows microenvironment-mediated dynamic switching and enhanced brain tumor targeting. *Theranostics* **2017**, *7*, 1875. [CrossRef] [PubMed]
156. Coluccia, D.; Figueiredo, C.A.; Wu, M.Y.; Riemenschneider, A.N.; Diaz, R.; Luck, A.; Smith, C.; Das, S.; Ackerley, C.; O'Reilly, M. Enhancing glioblastoma treatment using cisplatin-gold-nanoparticle conjugates and targeted delivery with magnetic resonance-guided focused ultrasound. *Nanomed. Nanotechnol. Biol. Med.* **2018**, *14*, 1137–1148. [CrossRef] [PubMed]
157. Wu, M.; Chen, W.; Chen, Y.; Zhang, H.; Liu, C.; Deng, Z.; Sheng, Z.; Chen, J.; Liu, X.; Yan, F. Focused Ultrasound-Augmented Delivery of Biodegradable Multifunctional Nanoplatforms for Imaging-Guided. *Adv. Sci.* **2018**, *5*, 1700474. [CrossRef] [PubMed]
158. Neuschmelting, V.; Harmsen, S.; Beziere, N.; Lockau, H.; Hsu, H.T.; Huang, R.; Razansky, D.; Ntziachristos, V.; Kircher, M.F. Dual-modality surface-enhanced resonance Raman scattering and multispectral Optoacoustic tomography nanoparticle approach for brain tumor delineation. *Small* **2018**, *14*, 1800740. [CrossRef]
159. Gao, X.; Yue, Q.; Liu, Z.; Ke, M.; Zhou, X.; Li, S.; Zhang, J.; Zhang, R.; Chen, L.; Mao, Y. Guiding brain-tumor surgery via blood–brain-barrier-permeable gold nanoprobes with acid-triggered MRI/SERRS signals. *Adv. Mater.* **2017**, *29*, 1603917. [CrossRef]
160. Lu, B.; Huang, Y.; Chen, Z.; Ye, J.; Xu, H.; Chen, W.; Long, X. Niosomal Nanocarriers for Enhanced Skin Delivery of Quercetin with Functions of Anti-Tyrosinase and Antioxidant. *Molecules* **2019**, *24*, 2322. [CrossRef]
161. Garrigue, P.; Tang, J.; Ding, L.; Bouhlel, A.; Tintaru, A.; Laurini, E.; Huang, Y.; Lyu, Z.; Zhang, M.; Fernandez, S. Self-assembling supramolecular dendrimer nanosystem for PET imaging of tumors. *Proc. Natl. Acad. Sci. USA* **2018**, *115*, 11454–11459. [CrossRef]

162. Narendra; Mehata, A.K.; Viswanadh, M.K.; Sonkar, R.; Pawde, D.M.; Priya, V.; Singh, M.; Koch, B.; Muthu, S.M. Formulation and in vitro evaluation of upconversion nanoparticle-loaded liposomes for brain cancer. *Ther. Deliv.* **2020**, *11*, 557–571. [CrossRef]
163. Ren, F.; Liu, H.; Zhang, H.; Jiang, Z.; Xia, B.; Genevois, C.; He, T.; Allix, M.; Sun, Q.; Li, Z. Engineering NIR-IIb fluorescence of Er-based lanthanide nanoparticles for through-skull targeted imaging and imaging-guided surgery of orthotopic glioma. *Nano Today* **2020**, *34*, 100905. [CrossRef]
164. Wang, X.; Tu, M.; Tian, B.; Yi, Y.; Wei, Z.; Wei, F. Synthesis of tumor-targeted folate conjugated fluorescent magnetic albumin nanoparticles for enhanced intracellular dual-modal imaging into human brain tumor cells. *Anal. Biochem.* **2016**, *512*, 8–17. [CrossRef] [PubMed]
165. Wang, X.; Yang, L.; Zhang, H.; Tian, B.; Li, R.; Hou, X.; Wei, F. Fluorescent magnetic PEI-PLGA nanoparticles loaded with paclitaxel for concurrent cell imaging, enhanced apoptosis and autophagy in human brain cancer. *Colloids Surf. B Biointerfaces* **2018**, *172*, 708–717. [CrossRef] [PubMed]
166. Du, C.; Liu, X.; Hu, H.; Li, H.; Yu, L.; Geng, D.; Chen, Y.; Zhang, J. Dual-targeting and excretable ultrasmall SPIONs for T 1-weighted positive MR imaging of intracranial glioblastoma cells by targeting the lipoprotein receptor-related protein. *J. Mater. Chem. B* **2020**, *8*, 2296–2306. [CrossRef] [PubMed]
167. Bagheri, S.; Yasemi, M.; Safaie-Qamsari, E.; Rashidiani, J.; Abkar, M.; Hassani, M.; Mirhosseini, S.A.; Kooshki, H. Using gold nanoparticles in diagnosis and treatment of melanoma cancer. *Artif. Cells Nanomed. Biotechnol.* **2018**, *46*, 462–471. [CrossRef] [PubMed]
168. Perry, H.L.; Botnar, R.M.; Wilton-Ely, J.D. Gold nanomaterials functionalised with gadolinium chelates and their application in multimodal imaging and therapy. *Chem. Commun.* **2020**, *56*, 4037–4046. [CrossRef]
169. Smilowitz, H.M.; Meyers, A.; Rahman, K.; Dyment, N.A.; Sasso, D.; Xue, C.; Oliver, D.L.; Lichtler, A.; Deng, X.; Ridwan, S.M. Intravenously-injected gold nanoparticles (AuNPs) access intracerebral F98 rat gliomas better than AuNPs infused directly into the tumor site by convection enhanced delivery. *Int. J. Nanomed.* **2018**, *13*, 3937. [CrossRef]
170. Zhao, L.; Li, Y.; Zhu, J.; Sun, N.; Song, N.; Xing, Y.; Huang, H.; Zhao, J. Chlorotoxin peptide-functionalized polyethylenimine-entrapped gold nanoparticles for glioma SPECT/CT imaging and radionuclide therapy. *J. Nanobiotechnol.* **2019**, *17*, 30. [CrossRef]
171. Meola, A.; Rao, J.; Chaudhary, N.; Sharma, M.; Chang, S.D. Gold nanoparticles for brain tumor imaging: A systematic review. *Front. Neurol.* **2018**, *9*, 328. [CrossRef]
172. Cho, J.-H.; Kim, A.-R.; Kim, S.-H.; Lee, S.-J.; Chung, H.; Yoon, M.-Y. Development of a novel imaging agent using peptide-coated gold nanoparticles toward brain glioma stem cell marker CD133. *Acta Biomater.* **2017**, *47*, 182–192. [CrossRef]
173. Lee, C.; Kim, G.R.; Yoon, J.; Kim, S.E.; Yoo, J.S.; Piao, Y. In vivo delineation of glioblastoma by targeting tumor-associated macrophages with near-infrared fluorescent silica coated iron oxide nanoparticles in orthotopic xenografts for surgical guidance. *Sci. Rep.* **2018**, *8*, 11122. [CrossRef]
174. Tamba, B.; Streinu, V.; Foltea, G.; Neagu, A.; Dodi, G.; Zlei, M.; Tijani, A.; Stefanescu, C. Tailored surface silica nanoparticles for blood-brain barrier penetration: Preparation and in vivo investigation. *Arab. J. Chem.* **2018**, *11*, 981–990. [CrossRef]
175. Ding, F.; Chen, Z.; Kim, W.Y.; Sharma, A.; Li, C.; Ouyang, Q.; Zhu, H.; Yang, G.; Sun, Y.; Kim, J.S. A nano-cocktail of an NIR-II emissive fluorophore and organoplatinum (ii) metallacycle for efficient cancer imaging and therapy. *Chem. Sci.* **2019**, *10*, 7023–7028. [CrossRef] [PubMed]
176. McHugh, K.J.; Jing, L.; Behrens, A.M.; Jayawardena, S.; Tang, W.; Gao, M.; Langer, R.; Jaklenec, A. Biocompatible semiconductor quantum dots as cancer imaging agents. *Adv. Mater.* **2018**, *30*, 1706356. [CrossRef] [PubMed]
177. Huang, N.; Cheng, S.; Zhang, X.; Tian, Q.; Pi, J.; Tang, J.; Huang, Q.; Wang, F.; Chen, J.; Xie, Z. Efficacy of NGR peptide-modified PEGylated quantum dots for crossing the blood–brain barrier and targeted fluorescence imaging of glioma and tumor vasculature. *Nanomed. Nanotechnol. Biol. Med.* **2017**, *13*, 83–93. [CrossRef] [PubMed]
178. Chan, M.H.; Liu, R.S.; Hsiao, M. Light/Ultrasound Responsive 750 nm-Emitted Non-toxic Indium Phosphide Quantum Dots Hybrid Nanobubble for Brain Tumor Imaging. *FASEB J.* **2019**, *33*, 662–666.

179. Tang, J.; Huang, N.; Zhang, X.; Zhou, T.; Tan, Y.; Pi, J.; Pi, L.; Cheng, S.; Zheng, H.; Cheng, Y. Aptamer-conjugated PEGylated quantum dots targeting epidermal growth factor receptor variant III for fluorescence imaging of glioma. *Int. J. Nanomed.* **2017**, *12*, 3899. [CrossRef]
180. Madhankumar, A.; Mrowczynski, O.D.; Patel, S.R.; Weston, C.L.; Zacharia, B.E.; Glantz, M.J.; Siedlecki, C.A.; Xu, L.-C.; Connor, J.R. Interleukin-13 conjugated quantum dots for identification of glioma initiating cells and their extracellular vesicles. *Acta Biomater.* **2017**, *58*, 205–213. [CrossRef]
181. Carvalho, I.C.; Mansur, A.A.; Carvalho, S.M.; Florentino, R.M.; Mansur, H.S. L-cysteine and poly-L-arginine grafted carboxymethyl cellulose/Ag-In-S quantum dot fluorescent nanohybrids for in vitro bioimaging of brain cancer cells. *Int. J. Biol. Macromol.* **2019**, *133*, 739–753. [CrossRef]
182. Perini, G.; Palmieri, V.; Ciasca, G.; De Spirito, M.; Papi, M. Unravelling the potential of graphene quantum dots in biomedicine and neuroscience. *Int. J. Mol. Sci.* **2020**, *21*, 3712. [CrossRef]
183. Ge, J.; Lan, M.; Zhou, B.; Liu, W.; Guo, L.; Wang, H.; Jia, Q.; Niu, G.; Huang, X.; Zhou, H.; et al. A graphene quantum dot photodynamic therapy agent with high singlet oxygen generation. *Nat. Commun.* **2014**, *5*, 4596. [CrossRef]
184. Jovanović, S.P.; Syrgiannis, Z.; Marković, Z.M.; Bonasera, A.; Kepić, D.P.; Budimir, M.D.; Milivojević, D.D.; Spasojević, V.D.; Dramićanin, M.D.; Pavlović, V.B.; et al. Modification of structural and luminescence properties of graphene quantum dots by gamma irradiation and their application in a photodynamic therapy. *Acs Appl. Mater. Interfaces* **2015**, *7*, 25865–25874. [CrossRef] [PubMed]
185. Shao, J.; Zhang, J.; Jiang, C.; Lin, J.; Huang, P. Biodegradable titanium nitride MXene quantum dots for cancer phototheranostics in NIR-I/II biowindows. *Chem. Eng. J.* **2020**, *400*, 126009. [CrossRef]
186. Liu, Y.; Liu, J.; Zhang, J.; Li, X.; Lin, F.; Zhou, N.; Yang, B.; Lu, L. Noninvasive Brain Tumor Imaging Using Red Emissive Carbonized Polymer Dots across the Blood–Brain Barrier. *ACS Omega* **2018**, *3*, 7888–7896. [CrossRef] [PubMed]
187. Guo, B.; Sheng, Z.; Hu, D.; Liu, C.; Zheng, H.; Liu, B. Through scalp and skull NIR-II photothermal therapy of deep orthotopic brain tumors with precise photoacoustic imaging guidance. *Adv. Mater.* **2018**, *30*, 1802591. [CrossRef]
188. Liu, Y.; Liu, J.; Chen, D.; Wang, X.; Zhang, Z.; Yang, Y.; Jiang, L.; Qi, W.; Ye, Z.; He, S. Fluorination Enhances NIR-II Fluorescence of Polymer Dots for Quantitative Brain Tumor Imaging. *Angew. Chem. Int. Ed.* **2020**, *59*, 21049–21057. [CrossRef]
189. Suárez-García, S.; Arias-Ramos, N.; Frias, C.; Candiota, A.P.; Arús, C.; Lorenzo, J.; Ruiz-Molina, D.; Novio, F. Dual T 1/T 2 Nanoscale Coordination Polymers as Novel Contrast Agents for MRI: A Preclinical Study for Brain Tumor. *ACS Appl. Mater. Interfaces* **2018**, *10*, 38819–38832. [CrossRef]
190. Huang, X.; Deng, G.; Liao, L.; Zhang, W.; Guan, G.; Zhou, F.; Xiao, Z.; Zou, R.; Wang, Q.; Hu, J. CuCo 2 S 4 nanocrystals: A new platform for multimodal imaging guided photothermal therapy. *Nanoscale* **2017**, *9*, 2626–2632. [CrossRef]
191. Ho, Y.N.; Shu, L.J.; Yang, Y.L. Imaging mass spectrometry for metabolites: Technical progress, multimodal imaging, and biological interactions. *Wiley Interdiscip. Rev. Syst. Biol. Med.* **2017**, *9*, e1387. [CrossRef]
192. Mathiyazhakan, M.; Wiraja, C.; Xu, C. A concise review of gold nanoparticles-based photo-responsive liposomes for controlled drug delivery. *Nano-Micro Lett.* **2018**, *10*, 10. [CrossRef]
193. Duan, Y.; Hu, D.; Guo, B.; Shi, Q.; Wu, M.; Xu, S.; Liu, X.; Jiang, J.; Sheng, Z.; Zheng, H. Nanostructural Control Enables Optimized Photoacoustic–Fluorescence–Magnetic Resonance Multimodal Imaging and Photothermal Therapy of Brain Tumor. *Adv. Funct. Mater.* **2020**, *30*, 1907077. [CrossRef]
194. Villa, C.; Campione, M.; Santiago-González, B.; Alessandrini, F.; Erratico, S.; Zucca, I.; Bruzzone, M.G.; Forzenigo, L.; Malatesta, P.; Mauri, M. Self-assembled pH-sensitive fluoromagnetic nanotubes as archetype system for multimodal imaging of brain cancer. *Adv. Funct. Mater.* **2018**, *28*, 1707582. [CrossRef]
195. Liu, X.; Du, C.; Li, H.; Jiang, T.; Luo, Z.; Pang, Z.; Geng, D.; Zhang, J. Engineered superparamagnetic iron oxide nanoparticles (SPIONs) for dual-modality imaging of intracranial glioblastoma via EGFRvIII targeting. *Beilstein J. Nanotechnol.* **2019**, *10*, 1860–1872. [CrossRef] [PubMed]
196. Yang, Z.; Du, Y.; Sun, Q.; Peng, Y.; Wang, R.; Zhou, Y.; Wang, Y.; Zhang, C.; Qi, X. Albumin-Based Nanotheranostic Probe with Hypoxia Alleviating Potentiates Synchronous Multimodal Imaging and Phototherapy for Glioma. *ACS Nano* **2020**, *14*, 6191–6212. [CrossRef] [PubMed]

197. Hallal, S.; Ebrahimkhani, S.; Shivalingam, B.; Graeber, M.B.; Kaufman, K.L.; Buckland, M.E. The emerging clinical potential of circulating extracellular vesicles for non-invasive glioma diagnosis and disease monitoring. *Brain Tumor Pathol.* **2019**, *36*, 29–39. [CrossRef]
198. Wang, H.; Jiang, D.; Li, W.; Xiang, X.; Zhao, J.; Yu, B.; Wang, C.; He, Z.; Zhu, L.; Yang, Y. Evaluation of serum extracellular vesicles as noninvasive diagnostic markers of glioma. *Theranostics* **2019**, *9*, 5347. [CrossRef]
199. Dumontel, B.; Susa, F.; Limongi, T.; Canta, M.; Racca, L.; Chiodoni, A.; Garino, N.; Chiabotto, G.; Centomo, M.L.; Pignochino, Y. ZnO nanocrystals shuttled by extracellular vesicles as effective Trojan nano-horses against cancer cells. *Nanomedicine* **2019**, *14*, 2815–2833. [CrossRef]
200. Rufino-Ramos, D.; Albuquerque, P.R.; Carmona, V.; Perfeito, R.; Nobre, R.J.; de Almeida, L.P. Extracellular vesicles: Novel promising delivery systems for therapy of brain diseases. *J. Control. Release* **2017**, *262*, 247–258. [CrossRef]
201. Jia, G.; Han, Y.; An, Y.; Ding, Y.; He, C.; Wang, X.; Tang, Q. NRP-1 targeted and cargo-loaded exosomes facilitate simultaneous imaging and therapy of glioma in vitro and in vivo. *Biomaterials* **2018**, *178*, 302–316. [CrossRef]
202. Kim, S.M.; Jeong, C.H.; Woo, J.S.; Ryu, C.H.; Lee, J.-H.; Jeun, S.-S. In vivo near-infrared imaging for the tracking of systemically delivered mesenchymal stem cells: Tropism for brain tumors and biodistribution. *Int. J. Nanomed.* **2016**, *11*, 13. [CrossRef]
203. Kalimuthu, S.; Oh, J.M.; Gangadaran, P.; Zhu, L.; Lee, H.W.; Rajendran, R.L.; Jeon, Y.H.; Jeong, S.Y.; Lee, S.-W.; Lee, J. In vivo tracking of chemokine receptor CXCR4-engineered mesenchymal stem cell migration by optical molecular imaging. *Stem Cells Int.* **2017**, *2017*. [CrossRef]
204. Pavon, L.F.; Sibov, T.T.; de Souza, A.V.; da Cruz, E.F.; Malheiros, S.M.; Cabral, F.R.; de Souza, J.G.; Boufleur, P.; de Oliveira, D.M.; de Toledo, S.R.C. Tropism of mesenchymal stem cell toward CD_{133}^{+} stem cell of glioblastoma in vitro and promote tumor proliferation in vivo. *Stem Cell Res. Ther.* **2018**, *9*, 310. [CrossRef] [PubMed]
205. Qiao, Y.; Gumin, J.; MacLellan, C.J.; Gao, F.; Bouchard, R.; Lang, F.F.; Stafford, R.J.; Melancon, M.P. Magnetic resonance and photoacoustic imaging of brain tumor mediated by mesenchymal stem cell labeled with multifunctional nanoparticle introduced via carotid artery injection. *Nanotechnology* **2018**, *29*, 165101. [CrossRef] [PubMed]
206. Lim, S.; Yoon, H.Y.; Jang, H.J.; Song, S.; Kim, W.; Park, J.; Lee, K.E.; Jeon, S.; Lee, S.; Lim, D.-K. Dual-Modal Imaging-Guided Precise Tracking of Bioorthogonally Labeled Mesenchymal Stem Cells in Mouse Brain Stroke. *ACS Nano* **2019**, *13*, 10991–11007. [CrossRef] [PubMed]
207. Hao, X.; Xu, B.; Chen, H.; Wang, X.; Zhang, J.; Guo, R.; Shi, X.; Cao, X. Stem cell-mediated delivery of nanogels loaded with ultrasmall iron oxide nanoparticles for enhanced tumor MR imaging. *Nanoscale* **2019**, *11*, 4904–4910. [CrossRef] [PubMed]
208. Wu, S.Q.; Yang, C.X.; Yan, X.P. A Dual-Functional Persistently Luminescent Nanocomposite Enables Engineering of Mesenchymal Stem Cells for Homing and Gene Therapy of Glioblastoma. *Adv. Funct. Mater.* **2017**, *27*, 1604992. [CrossRef]
209. Hsu, F.-T.; Wei, Z.-H.; Hsuan, Y.C.-Y.; Lin, W.; Su, Y.-C.; Liao, C.-H.; Hsieh, C.-L. MRI tracking of polyethylene glycol-coated superparamagnetic iron oxide-labelled placenta-derived mesenchymal stem cells toward glioblastoma stem-like cells in a mouse model. *Artif. Cells Nanomed. Biotechnol.* **2018**, *46*, S448–S459. [CrossRef]
210. Duan, Y.; Wu, M.; Hu, D.; Pan, Y.; Hu, F.; Liu, X.; Thakor, N.; Ng, W.H.; Liu, X.; Sheng, Z. Biomimetic Nanocomposites Cloaked with Bioorthogonally Labeled Glioblastoma Cell Membrane for Targeted Multimodal Imaging of Brain Tumors. *Adv. Funct. Mater.* **2020**, *30*, 2004346. [CrossRef]
211. Wang, C.; Wu, B.; Wu, Y.; Song, X.; Zhang, S.; Liu, Z. Camouflaging Nanoparticles with Brain Metastatic Tumor Cell Membranes: A New Strategy to Traverse Blood–Brain Barrier for Imaging and Therapy of Brain Tumors. *Adv. Funct. Mater.* **2020**, *30*, 1909369. [CrossRef]
212. Jia, Y.; Wang, X.; Hu, D.; Wang, P.; Liu, Q.; Zhang, X.; Jiang, J.; Liu, X.; Sheng, Z.; Liu, B. Phototheranostics: Active targeting of orthotopic glioma using biomimetic proteolipid nanoparticles. *ACS Nano* **2018**, *13*, 386–398. [CrossRef]

213. Grosu, F.; Ungureanu, A.; Bianchi, E.; Moscu, B.; Coldea, L.; Stupariu, A.L.; Pirici, I.; Roman-Filip, C.C. Multifocal and multicentric low-grade oligoastrocytoma in a young patient. *Rom. J. Morphol. Embryol.* **2017**, *58*, 207–210.
214. Wang, X.; Hu, Y.; Wang, R.; Zhao, P.; Gu, W.; Ye, L. Albumin-mediated synthesis of fluoroperovskite KMnF3 nanocrystals for T1-T2 dual-modal magnetic resonance imaging of brain gliomas with improved sensitivity. *Chem. Eng. J.* **2020**, *395*, 125066. [CrossRef]