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Nanoparticles as immunomodulators and translational agents in brain tumors

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Abstract

Introduction—Brain tumors remain especially challenging to treat due to the presence of the blood–brain barrier. The unique biophysical properties of nanomaterials enable access to the tumor environment with minimally invasive injection methods such as intranasal and systemic delivery.

Methods—In this review, we will discuss approaches taken in NP delivery to brain tumors in preclinical neuro-oncology studies and ongoing clinical studies.

Results—Despite recent development of many promising nanoparticle systems to modulate immunologic function in the preclinical realm, clinical work with nanoparticles in malignant brain tumors has largely focused on imaging, chemotherapy, thermotherapy and radiation.

Conclusion—Review of early preclinical studies and clinical trials provides foundational safety, feasibility and toxicology data that can usher a new wave of nanotherapeutics in application of immunotherapy and translational oncology for patients with brain tumors.

Keywords

Nanoparticles; Immunotherapy; Biomodulation; Clinical trials

Introduction

Brain tumors remain especially challenging to treat due to both anatomic and intrinsic factors [1, 2]. First, their location behind the blood–brain barrier (BBB) makes pharmacologic treatment challenging. Conventional therapies are primarily confined to local control options such as surgery and radiation [1, 2]. However, surgery alone is often not sufficient to cure these tumors and can cause damage to normal tissue architecture, while radiotherapy carries risks of radiation necrosis, vasculopathy, secondary malignancy, and adverse affects on cognition [1, 2]. Meanwhile chemotherapy has variable effectivity. Temozolomide, while standard therapy for glioblastomas (GBMs) in adults, maintains only ~ 20% of its blood concentration in the CNS [3]. Moreover, temozolomide is associated with systemic side effects, and has not been shown to demonstrably provide benefit against many

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glioma subtypes (e.g. pediatric high-grade glioma) [4, 5]. Thus, new therapies that overcome delivery limitations are paramount.

Immune therapies have produced impressive clinical benefits in the face of many treatment-resistant tumors [6–8]. However, immunologic treatment of brain tumors is complicated by barriers to delivery and their uniquely immune suppressive nature [9, 10], which have demonstrated an ability to withstand robust combination therapy with traditional chemotherapy, radiation therapy, surgery, and even newer immune therapies [11, 12]. Future treatment of brain tumors will require therapies that can initiate potent antitumor immune responses and eliminate the immunologic resistance of the tumor microenvironment (TME).

Nanotechnology may be a solution to both problems. Nanomaterials provide substantial flexibility of engineering to overcome traditional drug delivery barriers, and enable enhanced detection, delivery and treatment in a myriad of disease applications [13–17]. Their ability to access cancers through the enhanced permeability and retention effect has led to their use as modulators of pharmacokinetics for conventional drugs. Nanomaterials have also been leveraged to maximize particle delivery through the BBB [18–20]. Nanomaterials are particularly attractive in the setting of immune therapies. While increasing sophistication of engineering is enabling nanoparticles to deliver drugs with increasing efficiency, nanomaterials can also be engineered very simply for uptake by immune cells [21, 22]. Despite this promise, a dearth of cross-disciplinary expertise and concerns about their in vivo reactivity and toxicology have stunted the number of new nanoparticle (NP) technologies that have been actively translated into human use [23–26].

In this review, we will discuss approaches taken in NP delivery to treat brain tumors with a special focus on cell targets and injection methods (Fig. 1). We will also review the NPs currently used in human brain tumor trials. These data will provide foundational safety, feasibility and toxicology data that may usher a new wave of nanotherapeutics in application of immunotherapy and translational oncology.

Targeting approaches

NP based therapies have been designed for a variety of applications, reflected best in the diversity of their target cells. While the first NP therapies attempted to deliver chemotherapy directly to tumor cells to initiate cytotoxic effects, more recent approaches have targeted nanomaterials to peritumoral immune cells to modify the TME or enable application of heat to the entire tumor with photodynamic therapy, radiation therapy, or magnetic hyperthermia. More recent immunotherapy based approaches do not require NP passage across the BBB, but rather initiate peripheral education and activation of T cells that can then access the TME for induction of anti-tumor immunity. We begin this review with a discussion of each approach.

Tumor targeting NPs

Direct tumoricidal therapies must overcome the BBB to act specifically on tumor cells without toxicity to normal tissue. This has traditionally been achieved with synthetic NP components. For example, encapsulation of hydrophopic molecules (i.e. camptothecin) inside PLGA NPs increases delivery to brain tumors ten-fold leading to a survival benefit

in syngeneic GL261 murine tumors [27]. More recent approaches utilize biomimetic proteolipid NPs, which utilize glioma cell membrane proteins to penetrate the BBB [28]. In one study, this penetration enabled photodynamic therapy leading to a ~ 94% inhibition of tumor growth in an orthotopic model of C6 glioma [28].

Other NPs can be surface modified to enhance targeting to specific cells. For example, coating particles with granzymeb enabled superparamagnetic iron oxide NPs (SPIONs) to infiltrate tumors by binding to Hsp70 [29]. These particles initiated tumor cell death more effectively than granzyme-b alone, leading to prolonged survival in intracranial tumor models for U87 and H1339 [29]. Likewise, coating particles with a peptide recognized by PD-L1 enables NP localization to PD-L1-expressing glioma cells, simultaneously delivering payloads while blocking a critical immunoregulatory axis [30].

External-beam radiotherapy can be applied to further increase particle accumulation at the tumor site. For example, intracranial radiation before intravenous injection of iRGD-conjugated solid lipid-NPs loaded with PD-L1 and EGFR siRNA led to improved NP uptake in tumors and enhanced survival in GL261 preclinical models [31]. Alternatively, photodynamic therapy can also be harnessed to selectively activate NPs in desired locations. For example, administration of non-targeted indocyanine green-loaded phospholipid NPs produces therapeutic effects only in the areas that are exposed to near-IR light [32]. In one study, local application of photodynamic therapy in the TME increased infiltration of T cells and macrophages and increased expression of HSP70, leading to inhibition of tumor growth and extended survival in a rat 9L GBM [32]. This antitumor effect was absent in immunocompromised mice and was achieved without engineering NPs specifically to target tumors [32]. These “up-conversion” NPs nonspecifically accumulate, but are activated in the presence of photons to deliver photothermal therapy only inside tumors [33]. Although promising in preclinical models, photodynamic therapy faces challenges for clinical implementation due to the limited penetration depth of light through a thick tissue like the human skull. Further work may be necessary to specifically activate energy generation among particles through such a light-impenetrable material.

Targeting peri–tumoral immune cells

NPs can also be delivered to target peri-tumoral immune cells that are known to suppress immune activation, such as M2 macrophages. In one study, particles with a PbAE-mRNA polyplex core coated with PGA-Di-mannose to target M206 on macrophages were engineered to deliver mRNA encoding interferon regulatory factor-5 (IRF-5) and IKKβ (M1-polarizing transcription factors) [34]. Delivery of IVT-derived mRNA encoding these transcription factors was utilized to convert tumor associated macrophages to a pro-inflammatory M1 phenotype [34]. Although this treatment had limited effect as a monotherapy, NP-medi-ated delivery of these transcription factors elicited impressive tumor regression in an established brain tumor model when combined with radiation [34]. Similarly, albumin NPs containing transferrin receptor-binding peptide (T12) with mannose-targeting receptors crossed the BBB and converted M2 macrophages to an M1 phenotype, leading to slightly extended survival in intracranial models for U87 and GL261 [35]. Others have utilized inherent effects of particle components to modify macrophage

function. For example, gold-NPs with a polypeptide coating may activate peritumoral microglia and astrocytes to “wall off” tumor growth, effectively exploiting a mechanism utilized by microglia to protect the CNS from infection/inflammation [36]. NP formulations encapsulating chemotherapy (e.g. Nano-Dox) and magnetic NPs in combination with radiotherapy have also been shown to act directly on peritumoral cells such as M2 macrophages/MDSCs in the TME, leading to enhanced efficacy [37, 38].

Combination therapies

These TME modulators can reduce tumor growth as monotherapies but can also be applied to create a TME conducive to systemic immune attack. For example, lipid-NPs coated with the tumor-targeting peptide iRGD encapsulating both a phosphoinositide 3-kinase (PI3K) inhibitor to antagonize regulatory tumor cell populations and an α-GalCer to activate T cells synergistically reprogrammed the TME of intracranial tumors enabling adoptive cellular therapy treatments to prolong survival by ~ 50% in preclinical models [13]. In a similar approach, delivery of antisense oligonucleotides to TGF-beta via systemically administered polybutyl cyanoacrylate NPs coated in polysorbate-80 reduced TGF-beta production in tumors and facilitated improved response to whole tumor cell vaccines [39]. Likewise, gold-NPs enhance the effects of both chemotherapy with doxorubicin and immunotherapy with PD-L1 checkpoint inhibition [40].

More sophisticated multimodal particles have incorporated both targeting and imaging capabilities using a single particle. One group reported significantly improved survival in murine GL261 models using multimodal particles incorporating IONPs for MRI imaging, angiopep for BBB penetration/glioma cell targeting, siTGF-beta for immune modulation and temozolomide for tumor killing [41].

Targeting peripheral immune cells outside the TME

Using NPs to target peripheral cells that cross the BBB can be another avenue to indirectly deliver therapy across the BBB. Systemic targeting of peripheral immune cells outside the TME avoids barriers of intratumoral delivery. Our group has leveraged this approach using systemic non-targeted cationic liposomes bearing mRNA encoding tumor antigens [21]. We have shown that these tumor mRNA loaded NPs mediate potent antitumor adaptive immune responses against intracranial tumors [21], and may unlock effects of immune checkpoint inhibitors [22]. Other groups utilized similar approaches to demonstrate that liposomal delivery of microRNAs targeting the immune modulator STAT3 in monocytes/macrophages, achieves antitumor efficacy in mice and activity in canines [42]. Alternatively, subcutaneous administration of NP loaded DCs can also achieve tumor rejection. HSP-70-SPIONs within tumor lysate loaded DCs delayed tumor progression and increased survival in intracranial models for murine C6 glioma [43] while NP loaded DCs bearing grp170/neuritin peptide induced therapeutic levels of cytotoxic T cells [44].

Routes of administration

Although the simplest delivery method of any drug is direct injection into tumors, the unique biophysical properties of nanomaterials have also enabled access to the tumor environment with less invasive injection methods including intranasal and systemic delivery.

Intra–tumoral injection

Direct intratumoral injection of NPs can act at the disease site and remains superior for therapeutics that require high concentrations of particles in tumors. Most of these therapies seek to induce direct tumor killing. For example, direct injection of iron-oxide (IO) NPs produced by magnetotactic bacteria enables delivery of IONPs needed for tumor heating with alternating magnetic fields leading to inhibition of glioma growth in a U87 model [45]. Direct cytotoxicity can also be combined with immune modulation for prevention of tumor recurrence. This is evidenced by convection-enhanced delivery of lipophilic NPs delivering both Rh-188 with a CXCR4-blocking antibody [46] or direct injection of HDL-mimicking nanodiscs delivering both chemotherapy and immunotherapy with TLR-9 agonists [47]. Direct injection may limit systemic inflammatory response, and secondary side effects, and has been prioritized for virus-like particles derived from cowpea mosaic virus [48]. Although direct injection offers specification of an anatomic target, even greater precision can be achieved by engineering NPs with components to target specific cell types. For glial tumors, this can be achieved by modifying NPs to enhance binding to fibroblast growth factor-inducible 14 (Fn14R) in GBMs [49].

Intranasal

Intranasal injection has great potential for semi-local delivery but has not been utilized as frequently for therapeutic administration. While studies remain few, results appear promising. In one study, intranasal administration of chitosan-siGal-1 NPs produced survival benefits in glioma models by promoting an M1 phenotype in the tumor microenvironment (TME), enabling synergistic antitumor responses when coupled with either temozolomide or immunotherapy with dendritic cell vaccines and PD-1 checkpoint blockade [50, 51]. These early successes warrant further evaluation and utilization in future work.

Systemic delivery

Systemic delivery requires that therapies utilize active or passive uptake in the desired location. For therapies that act on the TME, this requires that particles cross the BBB and, in many cases, specifically infiltrate the tumor. Crossing a BBB composed of endothelial tight junctions is not easily achieved. While specific cell types can pass across the BBB through natural mechanisms, exploiting these can be difficult [52–54]. Since small lipophilic molecules may diffuse across the BBB, nanomaterials can be designed to penetrate or be engineered to cross [20, 55]. Alternatively, since tumors actively disrupt the BBB which is further compromised by standard of care radiotherapy, nanomaterials have preferential advantages in localizing to tumors [56, 57]. NPs can further exploit the leaky capillaries in tumors via the enhanced permeability and retention (EPR) effect, which enables NP retention in the TME [55–57]. Once in the TME, particles can deliver therapeutics to specific cell types based on their surface ligands and physical properties [55–57]. Thus, new nanomaterial designs can leverage these properties to preferentially target tumor cells, or peritumoral immune cells, after systemic administration.

Clinical trials

Clinical evaluation of NP based treatments for GBM has focused predominantly on direct and systemic administrations in adult patients. Despite recent development of many NP systems to modulate immune function in the preclinical realm, clinical work with NPs in GBM has largely focused on imaging, chemotherapy, thermotherapy and radiation. Here, we have grouped these studies based on injection method, treatment modality, and combination approaches, and summarized their results (Table 1).

Direct injection of chemotherapy loaded NPs

NP encapsulation can serve to increase drug penetration and delivery to tumor. Several delivery methods have been explored for increasing local drug concentrations, including convection enhanced delivery (CED) of liposomal chemotherapeutic formulations [58, 59]. CED is a minimally invasive technique for increasing local drug concentration through direct tumor cannulation and the application of continuous positive pressure, which can be achieved via syringe pump [59]. Despite the ability to increase local concentrations of chemotherapeutic agents, more information is needed regarding the distribution patterns and tumor coverage of NPs injected systemically versus via CED. In one small trial, ten canines with spontaneous gliomas were enrolled and treated with polymeric magnetite NPs (PMNPs) encapsulating temozolomide administered through image-guided CED [60]. Nine of the animals received the infusion without incident and 70% showed particle distribution within the tumor after delivery, suggesting CED can accurately target particles to sites of tumor [60]. Two animals showed clinical improvement, with one of them still living ~ 2 years after treatment [60]. In addition, analysis of the tumor microenvironment demonstrated necrosis, hemorrhage, and a substantial infiltration of phagocytic gitter cells [60]. As distribution of particles injected via CED is unpredictable and accurate tumor coverage is requisite for optimal response, similar methods for improving and assessing infusion accuracy should be applied in future clinical trials.

Direct injection of NPs for thermotherapy

Intratumorally injected magnetic-NPs can be used as a form of thermotherapy by heating injected particles in an alternating magnetic field. To ensure thermotoxicity is restricted to tumor tissue, PET-CT with an ^{18}F-labeled amino acid tracer has been shown to be useful for defining tumor volume and guiding thermotherapy [61]. In addition, radioactive PET-based imaging may reveal additional tumor tissue beyond that detected by MRI. In another early-phase thermotherapy study investigating the feasibility and safety of aminosilane coated iron-oxide NPs in recurrent GBM, 14 patients were administered the therapy followed by radiotherapy [62]. Overall, the treatment was found to be well-tolerated by all patients and produced some evidence of local tumor control [62]. Median survival was 14.5 months and compared favorably to historical controls, and one patient remained in remission 28 months after treatment [62]. This initial trial was followed by a phase II study evaluating thermotherapy in a larger cohort of 66 patients [63]. The treatment was again fairly well-tolerated and an increase in time-to-recurrence was noted [63]. Among those patients treated for recurrent GBM (59 of 66), median survival following initial tumor recurrence was 13.4 months (compared to 6.2 months for a historic control cohort), and 23.2 months for median

overall survival from initial diagnosis [63]. While 41% of patients had received some form of therapy prior to trial enrollment, only tumor volume at the initiation of the study was found to correlate with survival time [63]. It remains unclear whether thermodamage-induced inflammation was the primary mechanism for response in the prolonged survival outcomes observed relative to historic controls.

In a recent human trial, the “NanoPaste” treatment with SPIO nanoparticles was evaluated in 6 patients with a diagnosis of recurrent GBM [64]. In this trial, patients had their resection cavities coated with SPIO-NPs, followed by six 1-hour hyperthermia sessions administered through an alternating magnetic field [64]. Imaging, histopathology, and flow cytometric analysis revealed evidence of an inflammatory reaction seen by tumor flare reaction, prominent macrophage infiltration with NP uptake, increased CD3 + T cells, increased proportion of IFN-γ in T cells, and upregulation of HLA-DR and PD-L1 on myeloid cells and microglia in TME [64]. Although two patients had prolonged responses greater than 23 months, four required surgery to remove deposited NPs [64].

Systemic injection of chemotherapy loaded NPs

A NP based paclitaxel (nab-paclitaxel) treatment, which showed a significant improvement in survival of patients with primary breast cancer when compared with solvent-based paclitaxel (NCT01583426), has also been tested in brain tumors [65–67]. Treatment of advanced solid tumors with cycles of nab-paclitaxel in combination with lapatinib in a phase I clinical trial (NCT00313599) was fairly tolerable [65, 66]. Intravenously administered nab-paclitaxel was then combined with PD-L1 blockade (atezolizumab) for treatment of triple-negative breast cancer, including patients with brain metastasis [67]. An improvement in progression-free survival was noted with the addition of atezolizumab to standard nab-paclitaxel treatment (7.2 months vs. 5.5 months) when considering all treated patients. However, no significant survival difference was achieved in patients with brain metastasis in the intention-to-treat population [67]. Although preclinical evidence suggests that albumin-bound paclitaxel NPs may localize to tumors via enhanced transportation across endothelial cells, next generation therapeutics should include methods to evaluate these effects in human brain tumor patients [68].

Systemic injection of NPs for bio–imaging

NPs may currently have their most significant role in imaging. There is preclinical evidence that brain tumor margins could be enhanced on MRI from systemically administered ultra-small superparamagnetic iron oxide (USPIO) [69]. USPIO enhancement has been found to increase gradually, peak at 24 h, and remain sharp following administration [69]. This is distinct from gadolinium (Gd)-enhancement, which is immediate and begins decreasing within hours after administration [69]. Ferumoxytol is a clinical USPIO formulation that has been used extensively as an alternative to Gd-based contrast and found to be generally well-tolerated in multi-center review [70]. USPIO-enhanced MRI (FeMRI) has been suggested to function as a non-invasive imaging modality for monitoring macrophage infiltration in the CNS and atherosclerotic plaques [71]. As expected, FeMRI enhancement in CNS lesions was found to differ from that observed with GdMRI [72]. Additionally, FeMRI revealed

increased heterogeneity after ischemic brain injury, leading to a suggestion for its use to guide initiation of anti-inflammatory therapy [73].

Whether FeMRI functions to delineate normal tissue from tumor tissue based on leaky vasculature or the presence of macrophages remains unclear. Uptake of USPIO depends highly on context and may be influenced by whether a lesion is metastatic or primary and by the specific tumor type. For example, systemically injected USPIO was recently shown to aid in assessing inflammatory brain lesions and found to be taken up by astrocytes and TAMs (but not tumors) in preclinical tumor xenograft models [74]. Conversely, TAM-rich meningiomas did not show improved USPIO enhancement and tumor vasculature alterations may better associate with FeMRI signal in these tumors [75].

In retrospective analysis of 45 GBM patients, the mismatch between USPIO- and Gd-enhancement was found to effectively discriminate between true disease recurrence and pseudoprogression [76]. In patients with IDH-1 wildtype GBMs, increased mismatch ratios from FeMRI:GdMRI contrast signaled the onset of pseudoprogression and not recurrence; this pattern was reversed for patients with isocitrate dehydrogenase (IDH)-mutant GBMs [76].

Since FeMRI contrast enhancement may be affected by both macrophage infiltration and vascular changes, treatment-specific imaging changes should be systematically investigated. Unfortunately, a clinical trial investigating the effect of anti-VEGF therapy with bevacizumab on MR imaging with gadolinium and ferumoxytol was recently terminated due to insufficient enrollment (NCT00769093). Given the effects of immune infiltrates on contrast enhancement, the effect of checkpoint inhibitors and other immunotherapies on FeMRI and GdMRI enhancement should also be investigated to establish how immune modulation alters enhancement patterns on MRI.

Systemic injection of radiotherapy sensitizing NPs

In addition to NPs as contrast MRI agents and delivery vehicles for chemotherapy, radiosensitization is another potential NP application in brain tumors. While preclinical data suggests potential [77], clinical trials for NP-based radiosensitizers in brain tumors are ongoing. To this end, the NANO-RAD trial (NCT02820454) utilizes a gadolinium-based theranostic agent (AGuIX) in combination with whole brain radiation therapy [78]. This intravenously administered particle has a short half life of around 2.5 h in non-human primates [79] but preferentially accumulates in tumors via the EPR effect [78]. A phase-II trial is also planned (NCT03818386), as well as a trial coupling AGuIX with stereotactic radiotherapy (NCT04094077).

Future trials

Clinical trials evaluating NP based applications for brain tumors have so far focused on enhanced imaging contrast, chemotherapy delivery, thermotherapy and radiosensitization. These studies have largely considered tolerability and overall antitumor effects of these therapies, with less focus on particle pharmacokinetics and effects on intratumoral and peripheral immunity. Future studies should include therapies that combine multiple modalities and modulate intratumoral immunity or produce systemic immune responses.

These may include particles specially formulated for active targeting to tumor, for example with IL-13 receptor or anti-EGFRvIII moieties on the NP surface [80–82], or those specifically targeted to immune cells outside the tumor. In each of these studies, it will be important to assess particle localization in human patients and evaluate the effects of each therapy on the intratumoral and systemic immune response.

Conclusions

The treatment of intracranial tumors is complicated by poor BBB penetration of many therapeutic agents and by an inability to identify rogue tumor cells at infiltrating margins. NPs are particularly suited to address these limitations as they display enhanced tumor permeation and retention, enable increased drug delivery, act as contrast agents on MRI, and can sensitize tumors to radiotherapy. While clinical trials exploring these agents have been used in several applications, few have been successfully translated as treatment mainstays. However, given the boon of preclinical data and foundational feasibility and safety/toxicology features, newer studies can be rationally designed to unlock therapeutic activity in brain tumors. The difficulty in accessing the CNS from conventional methodologies may be addressed with new engineering designs allowing innovative NP formulations to tackle grand challenges in neuro-oncology.

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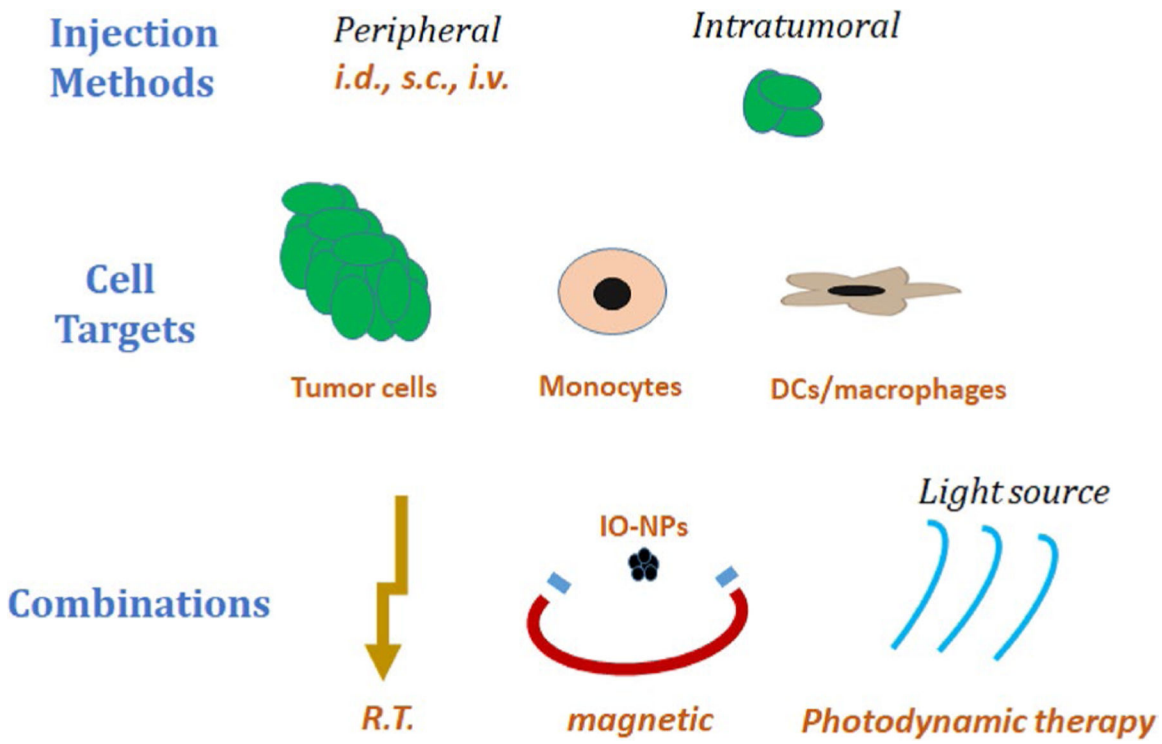

Fig. 1.

Summary of nanoparticle applications for treatment of brain tumors. Previous clinical work utilized systemic or intratumoral injections to deliver nanoparticles with direct cytotoxic activity on tumor cells either alone or in combination with radiation or magnetic hyperthermia. New preclinical avenues include intranasal nanoparticle delivery, the targeting of immune cells both inside the tumor and in the periphery, and photodynamic therapy to specifically mediate cell death at the tumor site. *i.d.* intradermal, *s.c.* subcutaneous, *i.v.* intravenous, *r.t.* radiotherapy, *IO-NP* iron-oxide nanoparticles

Table 1

Summary of clinical trials evaluating nanoparticles for treatment of brain tumors

Citation	Particle	Delivery	Mechanism	Phase	Result
Young et al. [60]	Polymeric magnetite NPs encapsulating temozolomide	CED	Chemotherapy	Large Animal Studies	7/10 canines displayed particle distribution within tumor. Potential clinical improvement in 2 animals
Maier-Hauff et al. [62]	Aminosilane coated iron-oxide NPs	Direct Injection	Thermotherapy	Phase I	All patients tolerated the infusion of magnetic nanoparticles and subsequent thermotherapy without complications.
Maier-Hauff et al. [63]	Aminosilane coated iron-oxide NPs	Direct Injection	Thermotherapy	Phase II	Median overall survival for recurrent (59/66) GBM patients was 13.4 months following first recurrence
Grauer et al. [64]	Aminosilane coated iron-oxide NPs	Coated resection cavity	Thermotherapy	Phase I	Evidence of an inflammatory reaction by histology Prolonged survival in 2/6 patients; 4/6 required surgical removal of particles
Schmid et al. [67]	Nab-paclitaxel	i.v.	Chemotherapy	Phase III	No significant survival difference seen between nab-paclitacel alone or nab-paclitacel plus atezolizumab groups in patients with brain metastasis
Enochs et al. [69]	Dextran-coated USPIO	i.v.	Imaging enhancement	Part of larger Phase III	USPIO enhancement increased gradually, peaking at 24 h, and remained sharp; distinct from gadolinium-based enhancement
Hamilton et al. [75]	Ferumoxytol	i.v.	Imaging enhancement	Pilot Study	Meningiomas with abundant TAMs did not show improved USPIO enhancement
Barajas et al. [76]	Ferumoxytol	i.v.	Imaging enhancement	Retrospective analysis	Study of 45 GBM patients demonstrates mismatch between USPIO- and Gd-enhancement to effectively discriminate progression from pseudoprogression
\Verry et al. [78]	AGuIX® (Polysiloxane matrix and gadolinium chelates based NP)	i.v.	Radiosensitizer and imaging enhancement	Phase I	Pending