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Approaches to physical stimulation of metallic nanoparticles for glioblastoma treatment

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ABSTRACT

Glioblastoma multiforme (GBM) is the most aggressive malignant brain tumor. Despite new knowledges on the genetic characteristics, conventional therapy for GBM, tumor resection followed by radiotherapy and chemotherapy using temozolomide is limited in efficacy due to high rate of recurrence. GBM is indeed one of the most complex and difficult cancer to treat mainly due to its highly invasive properties and the standard treatments are thus rarely curative. Major challenges in the treatment of GBM are the limitation of irreversible brain damage, the infiltrative part of the tumor which is the ultimate cause of recurrence, the difficulty of identifying tumor margins and disseminated tumor cells, and the transport across the blood-brain barrier in order to obtain a sufficient therapeutic effect for pharmalogical agents. Considering these limitations, this review explores the *in vivo* potential of metal-based nanoparticles for hyperthermia, radiotherapy and photodynamic therapy. This article describes and clearly outlines the recent *in vivo* advances using innovative therapeutic metallic nanoparticles such as iron oxide, silver, gadolinium and gold nanoparticles.

Contents

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1. Introduction

Over the past decade, there has been an explosion of research on glioblastoma multiforme (GBM) however, unfortunately only few studies have led to changes in patient outcome. Glioblastoma is indeed characterized by an extremely poor prognosis and has improved little despite maximum surgery, chemotherapy and radiotherapy [1]. Cytological heterogeneity of GBM makes the total eradication impossible due to residual cancer cells invading the *parenchyma*. Regardless of completeness of resection, infiltrative cells always remain following surgical cytoreduction, leading to recurrence. Depending on the surgeon capability to discriminate between cancer and non-cancer tissues, an extension of the resection without neurological deficits after surgery remains an essential component for improving patient prognosis [2]. For GBM treatment, magnetic resonance imaging (MRI) plays a central role in order to define and delineate the target volume for surgery and radiotherapy [3]. Moreover, GBM has a propensity to mutate leading to different genomic signatures [4].

Our motivation and rationale for suggesting this review was to argue that with the rapid development of nanomedicine for cancer applications, it is expected that newly developed metallic nanoparticles could have a major impact on GBM therapy and imaging-guided treatments. Recent progress in nanotechnology has indeed shed new light and prospect on cancer therapy and imaging due to unique physicochemical properties of inorganic nanoparticles [5,6]. While the potential of organic nanomaterials to capitalize delivery properties of cytotoxic agents for GBM treatment is widely documented [7] in contrast, inorganic nanoparticles and their biomedical applications remain relatively recent. Concerning GBM, nanomedicine approaches have been developed in the laboratories, with some technologies translated into the clinic. Without being exhaustive, the objective of this original review was to focus comments on the most significant advances concerning the interests of metallic nanoparticles to circumvent the main therapeutic challenges of GBM treatment. The review will target these opportunities by introducing biological and clinical features of brain tumors. This article is also motivated by the rapidly increasing number of *in vivo* publications investigating the potential of metallic nanoparticles, (i) to enhance external beam radiotherapy in a clinical setting and with recent developments using particularly gold, silver or gadolinium-based nanoparticles as theranostic agents, (ii) to induce hyperthermia ablation using magnetic nanoparticles such as new iron oxide nanoparticles or gold nanorods with laser induced hyperthermia, (iii) to promote a photodynamic effect with multifunctional silica-based hybrid nanoparticles, and (iv) to permeate the blood-brain barrier (BBB) using for instance, iron oxide nanoparticles. This review will also highlight *in vivo* recent advances and clinical prospects, focusing on the combination of imaging and therapeutic functions. Furthermore, the strategies for nanoparticles administration and translation to clinical application will be discussed. Lastly, the barriers towards clinical implementation of metallic nanoparticles will be suggested in order to bring better insight into strategies for developing the most feasible systems for treating GBM.

2. Understanding limitations of GBM standard treatment

Gliomas are heterogeneous tumors of the central nervous system and GBM is the most common and malignant type of glioma. Primary and secondary GBM correspond to two distinct disease subtypes, affecting patients of different age and developing through different genetic pathways. Primary GBM (*de novo*) indeed tends to occur in older patients (mean age, 55 years), whereas secondary GBM concerns younger adults (45 years of age or less) [8]. Primary GBM is associated with a high rate of overexpression or mutation of the epidermal growth factor receptor (EGFR), p16 deletions and mutations in the gene for phosphatase and tensin homologues (PTEN) [9], and secondary GBM describes genetic alterations involving the p53 gene, overexpression of platelet-derived growth factor A (PDGF-A) and its receptor [10].

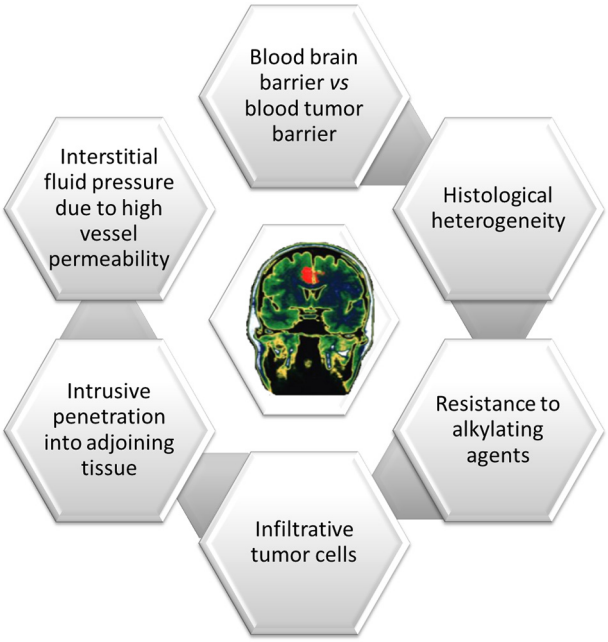

Fig. 1. Outline of main GBM challenges. Glioblastoma aggressiveness and deadliness is characterized by a heterogeneous set of neoplastic cells that are genetically unstable. Their histopathological characteristics include proliferative endothelial cells, increased blood vessel diameter, thickened basement membranes and high vessel permeability leading to interstitial fluid pressure. Glioblastoma is not only highly heterogeneous but also very infiltrative and is surrounded by peritumoral edema and inflammation. Glioblastoma exhibits indistinct tumor margins and therefore cannot be completely resected due to an intrusive penetration. Tumor-brain barrier is disrupted in all GBM patients nevertheless clinical evidences argue that it can remain intact (blood-brain barrier, BBB) in certain tumor areas. Alkylating agents, the mainstay of GBM treatment, damage DNA and induce apoptosis, however the cytotoxic activity of these chemotherapeutic agents such as temozolomide, is highly dependent on DNA repair pathways. Tumor cells deficient in mismatch repair are resistant to alkylating agents.

Glioblastoma is particularly difficult to treat because of the intrusive penetration of isolated cells into adjoining tissues, preventing the complete surgical removal from the brain. It is this invasive, infiltrative disease component which is the ultimate cause of recurrence, resistance and death (Fig. 1). Despite advances in the diagnosis and treatment of GBM, the median survival rate remains less than fifteen months [11]. Diagnosis is established by MRI, producing typically irregular contrast enhancement. The tumor lesion is usually surrounded by edema and the mass effect can be serious enough to induce herniation into the brain, raising an interstitial fluid pressure due to high vessel permeability (Fig. 1). Glioblastoma is widely infiltrative even if the contrast enhancement by T1-weighted imaging only illustrates the presence of a discrete border to the tumor lesion. It is well described that tumor cells extend microscopically several centimeters away from the major tumor lesion and that they are able to extend throughout large portions of the normal brain tissue known as *gliomatosis cerebri* [12].

Traditional GBM therapies include surgery, radiation therapy and chemotherapy. The goals of surgery range from a simple confirmation of diagnosis or an improvement of symptoms related to tumor mass effects to aggressive attempts to improve quality of life and to lengthen survival rates [2]. According to the famous paper published by Stupp et al. [13], newly diagnosed GBM patients with favorable Karnofsky performance scale and who undergo the standard of care, have a survival mean of approximately fifteen months. In addition, mean survival in patients undergoing surgical resection alone is significantly longer than in those who only underwent biopsy, 7 *versus* 3.5 months, respectively [14]. Hence, the main prognostic factor for these patients' survival remains the extent of the tumor resection and it is aimed at maximal safe resection as aggressive surgery prolongs patient survival [15]. Innovative approaches such as fluorescence-guided resection, laser

interstitial thermal therapy and intraoperative mass spectrometry were tested during the surgery.

Radiation therapy for GBM management consists of a 60 Gy total dose over 30 days, delivered as 2 Gy/day, 5 days/week, for 6 weeks using external megavoltage X-photon beams from a linear accelerator. Such treatment relies on the deposition of energy into the tumor tissue, typically when X-photons interact with atoms of biological tissue. Antitumor activity of ionizing radiations is based on the generation of secondary electrons and free radicals in oxygen-rich environments, which are responsible of cell damage such as DNA single- and double-strand breaks, membrane lipid peroxidation and protein oxidation. In particular, irradiated cancer cells are less capable of dealing with DNA damage and eventually decrease in mitotic activity or die. However, external photon radiotherapy is non-specific since a significant dose can be delivered to healthy tissue along the track of the photons, in front and behind the tumor zone and the doses needed to eradicate tumor cells are too important to be well tolerated by the surrounding healthy brain tissue. Clinical trials revealed a modest efficacy and moreover, there are several limitations using radiation therapy for GBM, including the risk of necrosis of the normal brain tissue. Treatment options at time of recurrence include reoperation, repeat radiation therapy, systemic therapy, or combined-modality therapy [16]. Thus, at clinically acceptable doses, treatment failures and recurrences after radiation therapy are systematic. Moreover, the brain tissue has a limited ability to repair itself, reducing the possibility of increasing irradiation doses. To improve local control and limit toxicity to normal brain tissue, novel imaging techniques are actively being explored to better define tumor extent and associated radiation therapy fields. Hyper fractionated radiotherapy has been associated with a survival detriment. For relapsed GBM, brachytherapy and stereotactic radiosurgery appear interesting therapies but tend to be associated with toxic events [17].

Currently, the standard treatment for newly diagnosed GBM consists of a chemoradiotherapy with temozolomide (at a dose of 75 mg/m^2 orally daily) and adjuvant temozolomide (150–200 mg/m^2/day per 5 days every 28 days for 6 cycles) [13]. Temozolomide, is an alkylating chemotherapeutic agent which has been introduced in 1999 (Fig. 2). This cytotoxic agent, once converted to its active form, damages DNA by methylating DNA guanine bases at the N7, N3, and O-6 positions. However, some tumor cells express O6-methylguanine DNA methyltransferase (MGMT), a dealkylating enzyme that removes methyl groups from the O6 position of guanine, inducing a resistance. Studies demonstrated that an inactivation of MGMT was associated with tumor regression and prolonged overall and disease-free survival in GBM [18]. Consistently, it was reported that methylation of specific sites in the MGMT promoter decreased protein expression and was associated with increased progression-free and overall survival. It is now admitted that the expression of a methylated MGMT promoter confers survival advantages [19,20]. Infiltrative tumor cells may also be less responsive to temozolomide as these cancer cells have decreased mitotic activity and may be further away from the tumor mass [19]. Most experts agree that targeting infiltrative tumor cells may improve patient survival and some agents specifically targeting infiltrative cells may be required in addition to standard chemotherapeutics. Nevertheless, the major difficulty comes from the lack of therapeutic agents able to penetrate the BBB (Fig. 1). This barrier indeed excludes the vast majority of cancer therapeutics from normal brain. The accumulation of radiographic contrast agent in GBM has popularized a belief that the BBB is disrupted in all GBM patients. However, overwhelming clinical evidence argues that there is also a significant tumor burden with an intact BBB in all GBM [21]. Thus, in case of GBM, according to the tumor zone considered, two configurations are finally possible: either an impaired BBB usually called blood-tumor barrier, characterized by a

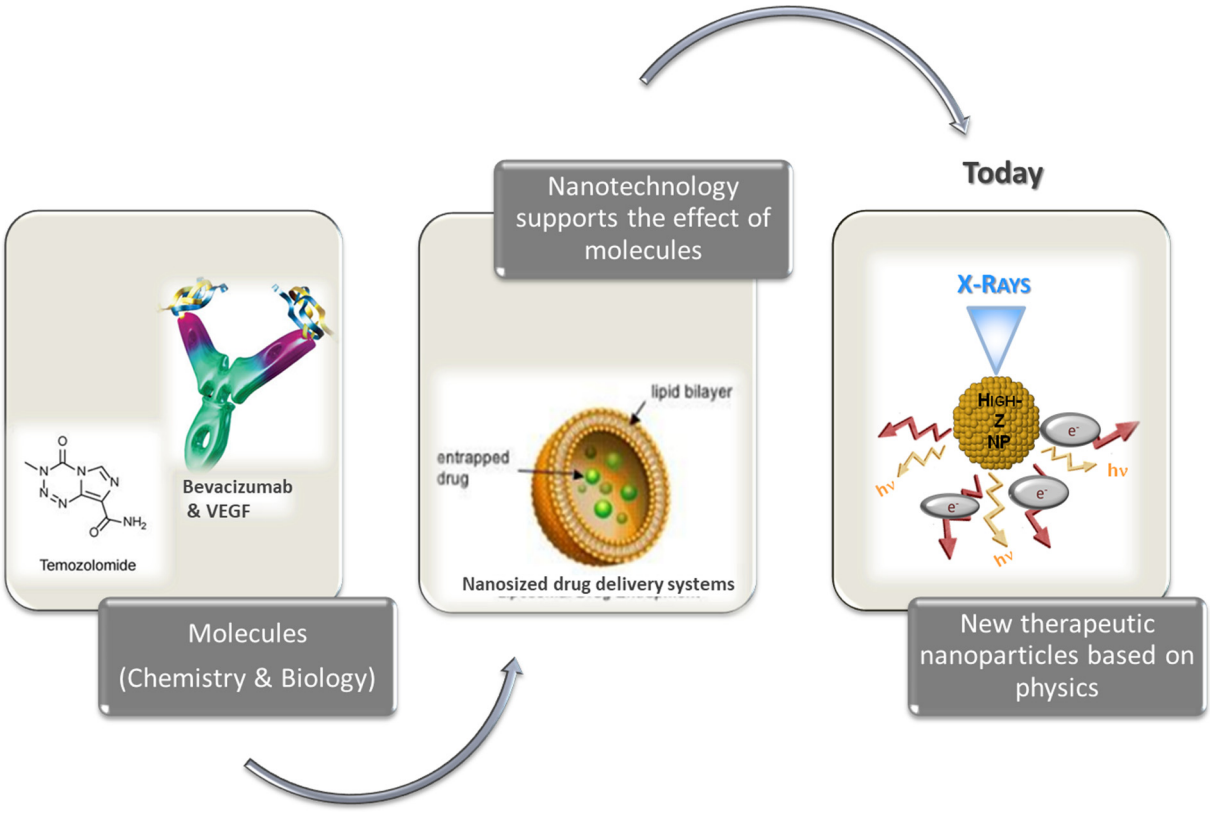

Fig. 2. Timeline of GBM therapy. After chemical innovations with temozolomide, an alkylating agent, followed by biological innovations using humanized IgG1 monoclonal anti-body such as bevacizumab, specific to all isoforms of VEGF-A, the first generation of nanoparticles has been developed to aim at optimizing delivery and controlling the release rate of drugs such as doxorobicin.Nowadays, we know the second generation of totally innovative nanoparticles as their therapeutic activity results from their intrinsic physical and photophysical properties.

fenestrated endothelium facilitating the arrival of anticancer agents to the tumor cells, or an intact BBB where the capillaries are closely bound by tight junctions and associated with pericytes and astrocytic feet, acting as a filter in order to be an obstacle for delivering therapeutic agents into the cerebral parenchyma. Knowing that cancer cells are located not only within the tumor mass but also in the peritumoral zone, therapeutic agents after intravenously injection can cross the BBB found in the central tumor zone and probably, unevenly, at the intermediate zone. However, some difficulties occur to cross the BBB at the macroscopically normal zone containing infiltrative cancer cells [22].

With the rapid development of nanotechnology for cancer applications, it is also expected that newly developed metallic nanoparticles could have a major impact on GBM therapy (Fig. 2). For instance, new generation of inorganic nanoparticles containing optical, thermal, and magnetic properties appears as very promising systems, offering new opportunities to overcome the limitations of current GBM management options in clinic.

3. Metal-based nanoparticles-enhanced radiotherapy

In neuro-oncology, the challenge faced by radiation oncologists remains the possibility of increasing radiation dose delivery into the tumor tissue to improve local control, while sparing normal brain parenchyma. Due to their high X-ray absorption capacities, interest in metallic nanoparticles has been growing steadily for the last decade, considering that inorganic nanoparticles with high atomic number (Z) can exert radio enhancing effects, in relation with the amplification of physical (electronic) processes.

3.1. Metal-based nanoparticles as radiation enhancer: how does it work?

Radiation treatments rely on the deposition of energy along the path of the incident radiation. When entering in contact with biological matter, high-energy ionizing radiations such as γ-ray, X-ray photons or charged particles lead into ionization of intracellular components and/or water molecule (named water radiolysis): the released secondary electrons (photoelectrons, Auger electrons and aqueous electrons) as well as the generated reactive oxygen species (ROS) cause cell damage resulting in direct and indirect cell death (Fig. 3). In case of X-ray photons, interaction with biological matter occurs through the Compton scattering or the photoelectric effect. The X-ray cross section, which refers to the probability of material interacting with radiation, is dependent on the Z number of the interacting atom. Considering that the chemical compositions (*i.e.* principally carbon, hydrogen, nitrogen, oxygen, phosphorus, and sulfur) of tumor and healthy tissues are similar, lethal effects of ionizing radiations concern indistinguishably healthy brain and GBM tissues. By contrast, high-Z elements due to their high electron density (bonding and unshared electron pairs) around the central atom can result in increased ionization of their surroundings when combined with ionizing radiation. Exploiting the enhanced permeability and retention effect (well known as the enhanced permeability and retention (EPR) effect), the preferential accumulation of high-Z nanoparticles into the tumor tissue results in creating a differential between tumor tissue and healthy parenchyma, and leads to an increased local dose deposition. After intracellular uptake of metal-based nanoparticles, an increased production of ROS and an amplification of DNA damage are expected to induce the death of irradiated cells (Fig. 3).

As recently reviewed by Retif et al., in the last ten years, many research programs have dealt with *in silico*, *in vitro* and *in vivo* evaluation of metal-based nanoparticles in radiation therapy, with very different experimental settings concerning irradiation and biological models [23]. Especially, the authors highlighted a wide heterogeneity between X-rays energy and irradiation setup, both parameters being able to greatly influence the radiosensitizing effect of metallic nanoparticles. A large number of metallic nanomaterials have been explored including gold, silver, platinum, hafnium, iron, bismuth, tungsten, zinc and rare earth elements (*e.g.,* gadolinium and cerium) (for review see [24]). Although the majority of investigations were focused on X-rays irradiation, tumor dose enhancement with high-Z nanoparticles was also reported using protons [25] and with brachytherapy [26].

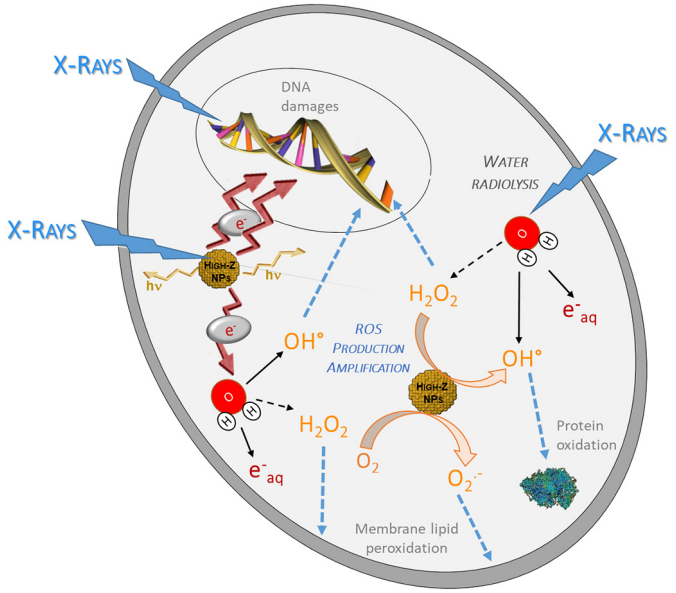

Fig. 3. Schematic illustration of radiotherapy enhancement by metal-based nanoparticles. When encounter the cell, incident X-photons beam induce excitations and ionizations of intracellular components, causing direct effects such as DNA damages (*e.g.* DNA simple- and double-strand breaks, DNA-protein crosslinks), and the water radiolysis leading to ROS production. Reactive oxygen species in turn alter cellular macromolecules inducing protein oxidation, membrane lipid peroxidation and indirect DNA damages. In presence of high-Z nanoparticles, the interactions between X-rays and nanoparticles result in an amplified production of secondary electrons and ROS, contributing to enhanced cytotoxic effects on irradiated cells.

3.2. Radiosensitization by metal-based nanoparticles for brain tumor treatment

In the context of GBM, gold-, silver-, and gadolinium-based nanoobjects remain the most frequently investigated and suggest the most promising prospects in clinical practice.

Following promising conclusions of an pioneering study on a murine mammary carcinoma model, Hainfeld et al. [27] evaluated the interest of a radiosensitization strategy using gold nanoparticles for brain tumor treatment. They mainly reported, for the first time, the *in vivo* potential clinical interest of intravenously injected core-shell 15 nm-sized gold nanoparticles for a X-ray imaging and an enhanced radiotherapy [28]. They demonstrated a preferential localization of gold nanoparticles into brain gliomas with a 19:1 tumor-to-healthy parenchyma ratio and a tumor uptake reaching 1.5% (weight of Au/weight of tissue), despite an inhomogeneous distribution throughout the tumor. The relevant accumulation of gold nanoparticles into the tumor tissue enabled a high-resolution for tumor imaging by computed tomography (CT). Then, application of a single dose of 30–35 Gy at 100 kVp after intravenous injection of nanoparticles (4 mg Au/g), resulted in 50% long-term (>1 year) survival compared to mice receiving only radiation. Despite wide sources of irradiation, energies and doses as well as great differences concerning the size and the coating of nanoparticles, several studies confirmed the benefit of gold nanoparticles to improve radiation therapy efficiency in GBM. Bobyk et al. actually evaluated the therapeutic efficiency of synchrotron stereotactic radiotherapy in combination with loco-regional administration of gold nanoparticles for the treatment of rats bearing orthotopic F98 glioma [29]. While an intracerebral administration of 15 nm gold nanoparticles (50 mg/mL, 250 μg Au) in rats bearing glioma was well-tolerated, a nanoparticles diameter

of 1.9 nm had an opposite impact and was found to be toxic, inducing an early death in 66% of cases. In this study, the median survival time reached 41 days for rats receiving a combined treatment (*i.e.* 15 Gy-irradiation, intracerebral injection: 50 mg/mL, 250 μg Au), while the median overall survival was 35 days for rats with an irradiation alone, that corresponds to a significant increase of 58% in life span. In parallel, Joh et al. [30] reported that PEGylated-gold nanoparticles (core size of 12 nm) exhibited a statistically significant reduced survival by clonogenic assay (with a dose-enhancement ratio of 1.3) for U251 GBM cell line. Moreover, using a model of mice bearing an orthotopic GBM, a combination of intravenous gold nanoparticles and 20 Gy-stereotactic irradiation increased survival of animals (mean survival reached 27.2 days for the combined treatment *vs* 18.3 for radiotherapy alone), despite the lack of optimization of the treatment regimen. Hainfeld et al. highlighted potential drawbacks of such approach that might be needed before a future clinical investigation: especially, *(i)* the poor whole-body clearance characterized by liver, spleen and even skin uptake of gold nanoparticles, and *(ii)* the high cost of gold nanomaterial [28].

Considering that the removal of gold nanoparticles by a renal excretion is widely expected compared to a hepatobiliary mode, Roux's team has designed small gold nanoparticles coated with dithiolated diethylenetriamine pentaacetic acid (DTDTPA), abbreviated as Au@DTDTPA, without undesirable accumulation in healthy tissue and removed from the body by a renal clearance after intravenous injection to healthy rats. Furthermore, these nanoparticles combined a radiosensitizing potential with the possibility of several imaging modalities such as X-ray imaging owing to the gold core, MRI and scintigraphy due to the DTDTPA shell enabling the immobilization of gadolinium ions (then abbreviated Au@DTDTPA-Gd_{50}) and radiometals for nuclear imaging [31,32]. Owing to gadolinium used as a contrast agent for MRI, the bi-metal nanoparticles Au@DTDTPA-Gd_{50} were very helpful in order to determine the best temporal window corresponding to the maximal accumulation of nanoparticles into the tumor tissue after an intravenous injection. Miladi et al. [33] evaluated the potential of these Au@DTDTPA-Gd_{50} nanoparticles for a radiosensitization *in vitro* and *in vivo* using a microbeam radiation treatment (MRT): a median survival time of 129 days was recorded only for the animals receiving the association Au@DTDTPA-Gd_{50} nanoparticles and MRT, compared to 72.5 days for irradiated rats.

Recently, the radiosensitizing potential of silver nanoparticles was reported on glioma models [34]. Authors compared the radiosensitizing effect of citrate-capped gold nanoparticles and citrate-capped silver nanoparticles with a core size of about 15 nm. After an intratumoral administration, both nanoparticles potentiated the *in vivo* antitumor effects of 8 Gy-irradiation at clinically relevant megavoltage energies (6 MV). Nevertheless, at the same mass concentrations, citrate-capped silver nanoparticles exhibited a more powerful radiosensitizing property. These observations corroborated previous results demonstrating radiosensitizing effects of silver nanoparticles. Indeed, after 200 days of follow-up, approximately a 40% of cure rate was found in C6 glioma-bearing rats treated by 10 or 20 mg of silver nanoparticles and 10 Gy-radiotherapy [35]. Likewise, Tamborini et al. developed silver nanoparticles entrapped inside chlorotoxin-functionalized nanovector: they demonstrated that the combination of 2 Gy-radiations with an intraperitoneally injection of these nanoparticles inhibited the tumor growth and progression whereas no inhibitory effect was observed for mice treated with either radiations or silver nanoparticles alone [36]. Taken together, these findings suggested the potential application of silver nanoparticles as a highly effective radiosensitizer for GBM treatment. However, their cytotoxicity reported in several *in vitro* studies using different cell lines and moreover, the uncertainty on the underlying mechanisms (for review [37]), may act as a brake for further preclinical and clinical developments.

With the aim of improving the precision and accuracy of radiation dose deposition into the targeted tumor volume, multifunctional nanoparticles were considered as well suited to achieve an image-guided radiation therapy. In this context, gadolinium-based theranostic agents have been developed for MRI-guided radiotherapy by the French group of O. Tillement. In 2011, Le Duc et al. confirmed the interest of ultrasmall gadolinium-based nanoparticles able to induce both a positive contrast for MRI and a radiosentizing effect in rats bearing intracerebral 9 L gliosarcoma treated with a microbeam radiation therapy [38]. The MRI follow-up of gadolinium positive contrast enhancement leads the authors to demonstrate a preferential localization of gadolinium-based into the tumor-containing brain hemisphere and their renal clearance. The median survival time reached 90 days for 9 L tumor-bearing rats treated by MRT, 20 min after gadolinium-based nanoparticles intravenous injection. Moreover, 50% of animals were still alive 100 days after tumor implantation. At the contrary, for animals who did not receive nanoparticles, the median survival time was 47 days without tumor cure. This study also highlighted the major role of the interval between irradiation and nanoparticles injection as animals' survival was drastically reduced (34 days) when MRT was performed only 5 min after injection, illustrating yet again the close link between nanoparticles tumor localization and treatment efficiency. Nowadays, a much attention is paid to the distribution of nanoparticles into the tumor microenvironment. Integrating this tumor microenvironment which includes abnormal vasculature and also extra cellular matrix, should be required for further development of GBM-targeted nanoparticles.

During the first few years after Sancey et al. investigated a new formulation of these gadolinium-based theranostic agents [39] named AGuIX® nanoparticles: these sub-5 nm-sized nano-objects are composed of polysiloxane and ~10 gadolinium chelates covalently grafted to the inorganic matrix. No presence of nanoparticles was measured in the healthy brain whereas a statistically significant accumulation of AGuIX® was reached in 9 L gliosarcoma orthotopic tumors after only 5 min post-i.v. injection. Biodistribution studies confirmed elimination by renal excretion as ideally expected for diagnostic and therapeutic purposes. In agreement with a great number of *in vitro* promising results demonstrating an interesting radiosensitizing potential of AGuIX® nanoparticles for different cell lines, irradiation energies and radiation sources, the *in vivo* intravenous injection of AGuIX® (10 mg of gadolinium) also induced a doubling of the median survival time of rats bearing 9 L orthotopic tumors when combined with MRT. Based on these promising results, Kotb et al. have conducted a proof-of-concept study aiming at validating such a strategy for the treatment of multiple brain melanoma metastases [40].The combined treatment induced a slight but statistically significant increase in animals' lifespan compared to mice without nanoparticle.

In summary, acquired preclinical data revealed that AGuIX® nanoparticles hold an interesting potential for MRI-guided radiotherapy as due to the gadolinium properties, they can serve as MRI contrast agent allowing tumor detection as well as radiosensitizer for radiation therapy. Complementary studies performed in rodents and non-human primates demonstrated no adverse effects even at high repeated doses [41]. All preclinical studies, taken together, supplied a strong rationale for clinical trials with AGuIX® begun in 2016 for patients with multiple brain metastases (NANORAD Phase 1B trial by NHTheraguix, referred in Clinical trials.gov as NCT02820454).

The entire community of radiation oncologists, radiobiologists and medical physicists look forward to the final results of this innovative clinical trial as it could be very useful to suggest other clinical studies for patients suffering from brain tumors.

4. Hyperthermia induced by metal-based nanoparticles

In addition to radiation therapies, alternative therapeutic approaches such as hyperthermia using metal-based nanoparticles, mainly magnetic or gold nanoparticles, have produced very promising *in vivo* results and are the subject of ongoing clinical investigations. The use of magnetic nanoparticles for hyperthermia was first attempted

as a cancer treatment in 1957 [42]. However, despite more recent advancements, magnetic hyperthermia therapy has still not become part of the standard of care for cancer treatment even if it appears especially attractive for GBM treatment. Some challenges such as an accurate thermometry within the tumor volume and a precise tumor heating, preclude its widespread application as a treatment modality. Current limitations and future prospects will be described.

4.1. What is hyperthermia?

Hyperthermia, also known as thermotherapy, is not strictly speaking a new cancer treatment. A lot of research has already demonstrated that elevated temperature could damage and destroy cancer cells mainly by altering proteins and structures within the tumor tissue. Membranes are extremely sensitive to heat stress related to their molecular composition of phospholipids and proteins. Hyperthermia can indeed promote cell membrane permeability, leading for instance, to increasing drug delivery into tumor cells, and vascular permeability in endothelium and improving drug diffusion into the tumor tissue. It is also well known that at high doses, heat induces cell death that can be immediate for extreme doses. Depending of the selected target temperature, intracellular and extracellular effects of hyperthermia include for instance, protein misfolding, induction of apoptosis process, changes in pH, reduced perfusion and oxygenation of the tumor tissue [43]. Hyperthermia also induces disassembly of the cytoskeleton, enlarges the tumor pores, alterations of integrin cytoskeleton network and *anoikis*. Moreover, hyperthermia was also reported to induce DNA double-strand breaks due to the denaturation and dysfunction of heat-labile repair proteins or to the precipitation of denatured proteins onto nuclear chromatin structures, generating a barrier which limits repair enzymes to reach damage sites. Its significant advantages seem to be in combination therapy with lower doses of chemotherapy or radiotherapy, leading to more effective treatment with fewer unwanted side effects in which hyperthermia can sensitize tumor cells to chemotherapeutic drugs, or radiation therapy by altering cytoskeleton re-organization, enhancing membrane permeability and inhibiting DNA repair [44]. Numerous clinical trials have studied hyperthermia in combination with conventional therapies and many of these studies, but not all, have highlighted a statistically significant reduction in tumor size when it was combined with other standard treatments. For example, adjuvant interstitial brain hyperthermia, given before and after brachytherapy boost, after conventional radiotherapy has demonstrated to improve survival of patients with GBM [45].

4.2. What are the different physical sources of hyperthermia in case of GBM treatment?

For clinical applications, three different approaches are available: local, regional and whole-body hyperthermia, depending on the type of cancer, its location and its stage. For GBM, techniques used to achieve a localized hyperthermia include radiofrequency, ultrasound, magnetic field and laser. More traditionally, hyperthermia was performed using external devices in order to transfer thermal energy to cancer tissues, either by light exposure or electromagnetic waves. However, each of both methods suffers from limitations, including low heat diffusion into the tumor tissue, an excessive heating of healthy tissue and a thermal under dosing in the targeted region. Interstitial techniques were also suggested to treat deep tumors such as brain tumors, allowing the tumor to be heated to higher temperatures than external techniques. Imaging techniques, such as ultrasound or MRI, were also applied to make sure that the fiber was properly positioned within the tumor. Laser interstitial thermotherapy appears as a novel technique, allowing an ablation *via* a stereotactic implantation of an optical fiber. It is monitored with a real-time MRI thermometry, and a dedicated software is available to sum the regions heated sufficiently to achieve thermal ablation. Laser thermotherapy has already been reported for glioma treatment, metastases, and radiation necrosis [46]. In a prospective clinical trial on the use of laser interstitial thermotherapy for recurrent GBM, there was a trend towards improved survival in patients treated with higher thermal doses [47] Progression-free survival was also improved in patients with high grade gliomas in difficult-to-access areas when there was more complete coverage of tumor volume by thermal ablation treatment lines [48].

4.3. Magnetic hyperthermia using iron oxide nanoparticles

In magnetic hyperthermia, heat results from a local accumulation of magnetic nanoparticles and subsequent application of an external alternating magnetic field. When they are exposed to alternating magnetic fields, in principle all magnetic materials could generate heat *via* hysteresis losses. Their heating capacity depends upon the material intrinsic properties and the alternating magnetic fields parameters. However, for magnetic nanostructured materials, the heating efficacy is based on a more complex relationship between the intrinsic time-dependent relaxation processes of the nanoparticle magnetic moments and the time-scale of the oscillating alternating magnetic field [49].

In the last decade, several types of iron oxides have been explored to synthesize magnetic nanoparticles, including magnetite (Fe_3O_4), hematite (α-Fe_2O_3), and maghemite (γ-Fe_2O_3 and β-Fe_2O_3) [50]. Magnetic nanoparticles remain the most frequently investigated because of their biocompatibility and among them, superparamagnetic iron oxide nanoparticles (SPIONs) remain the nanoparticles of choice in relation to their unique optical and magnetic properties [51]. Due to their low toxicity, iron oxide nanoparticles have been first applied as contrast agents for MRI and more recently validated for magnetic hyperthermia. In magnetic hyperthermia, iron oxide nanoparticles can be injected into the tumor tissue and heated at 41–50 °C under the application of an alternating magnetic field [52,53]. In Europe, magnetic hyperthermia therapy using iron-oxide (magnetite) nanoparticles was approved in 2012 as an adjuvant therapy for recurrent GBM in combination with stereotactic radiotherapy. Under alternating magnetic field application, these nanoparticles are locally administered, leading to an increased survival of seven months in comparison with standard treatments. A stereotactic radiotherapy at 6 MV with a biologically equivalent median dose of 30 Gy, was performed on the planning target volume, fractionated as 5×2 Gy per week. Radiotherapy was realized immediately before or after the intratumoral thermotherapy sessions. The hyperthermia treatment generally consisted of six semi-weekly sessions, and each thermotherapy session lasted 1 h [54]. In this approach named Nano-Cancer®therapy, biocompatible nanoparticles (iron-oxide magnetite (Fe_3O_4) of ~12 nm diameter with an aminosilane coating), were directly injected into the tumor tissue (iron concentration of 112 mg/mL) and subsequently stimulated by an alternating magnetic field (100 kHz, MagForce Nanotechnologies) to generate heat. Intratumoral thermotherapy was regarded as safe and well tolerated. During thermotherapy, body temperature exceeded 38 °C only in 9.1% of patients and the median peak temperature measured within the tumor zone sessions was 51.2 °C. This study likewise demonstrated that this new therapeutic approach, in conjunction with fractionated stereotactic radiotherapy, was clinically effective, highlighting that intratumoral thermotherapy seemed particularly efficient in combination with radiotherapy in order to amplify its effects. Moreover, in contrast to radiotherapy which is subject to cumulative dosage limits, the thermotherapy sessions may be repeated without any inherent limit. The combination of intratumoral hyperthermia and temozolomide would also present a promising approach for GBM treatment.

Compared with other thermotherapies, magnetic hyperthermia, in which iron oxide nanoparticles are administered into the tumor tissue, requires lower heating temperatures of 43–50 °C to be efficient. To improve its the efficacy, better heating properties were suggested and developed using stable magnetic single domain iron oxide nanoparticles which were either doped with cobalt to increase magnetocrystalline

anisotropy, or possessed a large size, leading to ferrimagnetic properties [55]. Instead to add a toxic compound into nanoparticles composition, an original approach was suggested using magnetotactic bacteria to synthesize large nanominerals called magnetosomes. In comparison with SPIONs, magnetosomes are better crystallized, yielding improved magnetic properties. Another major advantage comes from their arrangement in chains, preventing them from aggregation, a useful characteristic for an *in vivo* use since it avoids embolism and allows a more homogeneous heating of the tumor tissue. Chains of magnetosome were injected into mice bearing GBM tumors and activated using several sessions of an alternating magnetic field in order to allow a moderate rise in temperature (<4 °C) during the successive treatment sessions [56]. Despite a complete disappearance of tumors, it was nevertheless observed that following the application of the alternating magnetic field, endotoxins initially present at the surface of the magnetosome chains, were released, leading to an activation of the natural immune system. To make them nontoxic, naked magnetosome minerals were coated with poly-L-lysine to obtain an injectable suspension compatible for an *in vivo* use. It was then possible to heat the tumor tissue until full disappearance in all treated mice within a period one month after the start of the treatment. Very interesting and promising results were obtained for partially immune-deficient and immunocompetent mice [57,58],demonstrating that a major therapeutic effect could be obtained on the entire tumor whereas magnetosomes occupy only a part of it. Since GBM are diffuse and therefore very difficult to distribute in a homogeneous way with nanoparticles, this property will remain crucial for ensuring the best efficiency of hyperthermia. It has also been highlighted that magnetosome residence time into the tumor area was longer than in the case of chemical nanoparticles, allowing a prolonged reactivation of the treatment, which is another interesting feature for curing GBM. Researchers also plan to conduct clinical trials for GBM once magnetosome product formulation will be fully finalized, regulatory toxicity tests completed, and treatment parameters optimized.

4.4. Laser induced hyperthermia using gold nanoparticles

Another approach to improve the spatial selectivity is tumor tissue photothermal labeling using gold nanoparticles. Gold nanorods exhibit optical properties depending on size and aspect ratio. Surface plasmon resonance is the resonant oscillation of free electrons onto the nanoparticle surface induced by incident light using an infrared laser. Surface plasmon resonance indeed results of interaction between electrons in a conduction band of gold atoms and electric field components of incident electromagnetic radiation. The absorbed photon energy is converted to heat *via* electron-phonon relaxation, and is transferred into the nanoparticle [59]. This process is called plasmonic photothermal therapy. This interaction results in unique thermal, optical and electrical properties frequently related for nano-photosensitizers. In the context of GBM, plasmonic photothermal therapy remains mainly suggested to induce temporary disruption of the peritumoral blood-brain barrier and also in order to increase drug delivery in cancer chemotherapy in addition to cytoreductive ablation [60]. By exposing gold nanorods to laser irradiation near their plasmon-resonant absorption band, it remains possible to induce a local heating only for the nanoparticles accumulated into the tumor tissue without harming surrounding healthy tissues. The spectral tuning of these nanoparticles resonance is achieved to the therapeutic optical window from750 to 1100 nm. It is also crucial to obtain the desired ratio between the absorption and scattering efficiencies by variation in the nanoparticle size, shape and structure. Precise control over the local temperature distribution remains the key factor that should be taken into account in the context of enhanced photothermal therapy efficiency. Laser heating can result in both tumor necrosis and possibly apoptosis or unfortunately in accelerated tumor growth, depending on the accuracy of heating and on the rise in tumor temperature on illumination with laser light. Specifically, heating up to 39 to 45 °C may lead to the acceleration of biological reactions accompanied by the production of heat shock proteins and by an intense tumor, pointing out the crucial impact of temperature monitoring. [61]. *In vivo*, an interesting advantage of photothermal therapy using gold nanoparticles appears to be the reduction in the laser power required to promote a local hyperthermia. For example, it was reported that only three min of irradiation at 3.0 W were sufficient to thermally ablate the tumors after an intravenous administration of gold nanoparticles (nanoshells) [62]. Regarding the special photophysical features of gold nanorods, they were suggested as a novel photothermal therapy for treatment of GBM. This feature was also suggested in many studies to improve photodynamic therapy in the treatment of GBM [63,64].

Gold nanorods also have attracted great interest due to a superior biocompatibility. They were also conjugated with biomolecules that carry sequences that can bind to cancer markers. For instance, Choi et al. suggested PEGylated gold nanorods conjugated with an RGD sequence to specifically bind $\alpha v\beta 3$ integrins expressed on GBM cells [65]. This study demonstrated that RGD-gold nanorods were able to circulate for prolonged periods of time and bind to GBM cell surface.

4.5. Radiofrequency waves for tumor tissue ablation using nanoparticles

Application of radio frequency waves is one of the more common thermal therapy approaches in oncology. It was suggested as an adjuvant therapy mainly in order to enhance the cytotoxic effects of chemotherapy and radiotherapy. Radiofrequency waves can effectively penetrate into deep sites, being a great advantage in treating deep-seated tumors such as GBM. Despite other advantages, the current radiofrequency ablation methods suffer from limitations such as the insertion of wide probe into the tumor site, a non-specific and a non-uniform heating resulting in hot spots within overlying healthy tissues, an inaccuracy of needle placement, and an incomplete destruction for a wide range of solid tumors. In order to circumvent some of these drawbacks, radiofrequency ablation using metal-based nanoparticles, was suggested to maximize thermal damage to the tumor site and also to preserve the safety of the surrounding tissue [66]. These metallic nanoparticles were composed with high electronic materials such as gold. When they were exposed to radiofrequency waves, a vibrational energy release was induced leading heating ~100 μm around the nanoobject. While standard radiofrequency ablation has been involved in human clinical trials for GBM treatment [67,68], further investigations using other metal-based nanoparticles are warranted.

4.6. Ultrasound hyperthermia using metallic nanoparticles

Like other nanotechnology-based hyperthermia strategies, metallic nanoparticles can play a role comparable to that of sensitizers, and allow tissues to absorb the energy of ultrasonic waves. The presence of nanoparticles in the acoustic field affects both the thermal and mechanical interactions of ultrasound, improving ultrasonic heating and cavitation. Due to their high thermal conductivities, metallic nanoparticles can enhance the effective thermal conductivity. It is clear that a tumor can be heated more rapidly if loaded using nanoparticles with higher thermal conductivity. Additionally, it is obvious that smaller nanoparticles have a higher thermal conductivity because of their higher surface to volume ratio. The few *in vivo* studies are actually available related to ultrasound hyperthermia methods using metal-based nanoparticles but potential is enormous [66].

In conclusion, conventional hyperthermia with external devices was applied *in vivo* for GBM treatment but suffers from temperature control, leading to overheating and damage of healthy tissue and/or dissipation of heat from the tumor tissue. Interstitial techniques were suggested to treat brain tumors, allowing the tumor to be heated to higher temperatures than external techniques. Imaging techniques may be applied to optimize the optical fiber position. Challenges include moderate to low absorption rates, monitoring of temperature distribution, self-regulation of heating, and precise control of intratumoral temperature.

Magnetic and gold nanoparticles are the most promising nanoparticles. Hyperthermia with magnetic nanoparticles enables controlled heating. Nanoparticle-based hyperthermia can be undoubtedly suggested for improving its direct and combined therapeutic effects. Gold nanorods encompass better properties than gold nanospheres, including superior biocompatibility and higher light absorption per unit volume. When gold nanorods were *in vivo* tested and irradiated with near infrared laser light, they induced statistically significant thermal ablation of tumor cells.

5. Photodynamic therapy using metal-based nanoparticles

Photodynamic therapy (PDT) appears as an innovative technology being investigated to fulfill the need for a targeted cancer treatment that may reduce recurrence and extend survival with minimal side effects. The therapeutic effects of visible light have been known since antiquity. Egyptians already used light combined with natural substances to treat skin diseases. In 1904 von Tappeiner assumes that oxygen was essential for the process and coined the term of "photodynamic reaction" [69]. In 1948, Figge et al. [70] suggested the possibility of using hematoporphyrin to locate tumor areas in humans. But it was not until 1970s, with Dougherty's experiments, that PDT really took off. Hematoporphyrin-derived and red light exposure have shown interesting results in preclinical and clinical studies [71]. A number of clinical studies, including phase III randomized prospective clinical trials of PDT, have been reported, using different technologies such as interstitial PDT (iPDT) and intraoperative PDT. Interstitial PDT offers a localized treatment approach in which improvements in local control of GBM may result in significant improved survival [72–74]. Several photosensitizers have been used, including porfimer sodium (Photofrin®), 5-aminolevulinic acid (5–5-ALA, Gliolan®) and *m*-tetrahydroxyphenylchlorin (*m*THPC, temoporfin, Foscan®) and benzoporphyrin derivative monoacids ring A (BPD-MA, verteporfin, Visudine®). In GBM context, PDT appears to be a very promising approach, not only alternative but also complementary to conventional therapies to prevent tumor local recurrence and improve survival rate with minimal side effect [75]. The concentration of the photosensitizing agents in some tumors reaches interesting ratios compared to normal brain cells. However, the reported tumor-to-healthy brain ratio depends on the histological grade of the tumor. The higher the grade of the tumor was, the higher the concentration of the photosensitizer in the tumor. The analysis stratified for pathology suggested by *Muller and Wilson* in 2006, demonstrated that the median survival post-PDT of newly diagnosed GBM patients was 15.2 months with 1- and 2-year survival of 65% and 16%, respectively. In this pertinent study, there was no difference in the high and low dose groups involving recurrent GBM patients, however the literature indicates that a higher dose might be beneficial, but there are no other controlled data than that one in this randomized study [76].

5.1. How does PDT work?

Compared to radiotherapy, the light irradiation used in PDT is less energetic so is harmless but it cannot penetrate deeply enough into the tissue because most tissue chromophores absorb visible light commonly used in clinical practice. For instance, the penetration depth of 630 nm light in brain-adjacent-to-tumor is appreciatively 2.5 mm. As the effective PDT distance is *ca.* 3 times the penetration depth, 630 nm light would appear to be inadequate for eradicating tumor cells in the brain-adjacent-to-tumor as the treatment volume only extends to approximately 0.75 cm from the light source. An obvious strategy to increase the treatment volume is to use a photosensitizing agent that absorbs longer wavelengths where light penetration in tissue is higher. Another alternative strategy for increasing the therapeutic volume is to increase the overall treatment time. However, it seems difficult to achieve with traditional "one-shot" intraoperative PDT regimes. High fluence rates have been shown to reduce intra-tumor oxygen levels and, thus, to decrease PDT efficiency [77]. Other different methods of light application have been used, including stereotactically inserting optical fiber for iPDT, filling the tumor cavity with a light-diffusing medium, such as lipid solution, to spread the light evenly throughout the tumor cavity, or using a balloon-like device filled with light-diffusing medium for intraoperative cavity photo-illumination. In this context, its applicability remains widely limited by light penetration in tissues.

Moreover, optimization of PDT modalities must take into account numerous *phenomena*, regarding one or several main factors (photosensitizer, light, oxygen) involved in the treatment efficiency. A specific dosimetry remains challenging owing to their nonlinear interactions. Light penetration into the target tissue depends on its specific optical properties. If the tissue is hypoxic or becomes hypoxic as a result of treatment, the yield of singlet oxygen $^1O_2$ will be lower than expected. To further complicate matters, photosensitizer concentration, light penetration and tissue oxygenation can vary during treatment and one parameter can influence the other.

The application of nanoparticles in PDT has been a major stride forward in resolving some of the challenges associated with classic photosensitizers. Depending on the type of nanoparticles and mode of attachment of photosensitizer (loading or grafting), they can have some advantages such as the increase of the amount of photoactivatable molecules delivered to the tumor tissue, the lack of a premature release of photosensitizer and nonspecific accumulation into normal tissues. The vast majority of inorganic nanoparticles can improve photosensitizers' aqueous solubility, they can take advantage of the EPR effect and their surface can be modified with functional groups or targeting agents. Metallic nanoparticles can be designed as multifunctional nanoplatforms carrying multiple components such as imaging agents (very useful in order to optimize the drug-light interval and the optical fiber positioning), chemo-drugs and targeting ligands.

5.2. Metal-based nanoparticles for PDT and imaging

Bechet et al. highlighted that iPDT for GBM is a pertinent complementary approach to conventional therapies such as radiotherapy and that, imaging plays an essential role to treatment planning, dosimetry, monitoring and outcome assessment [75]. Recently it was demonstrated in *in vivo* models (rats bearing GBM) that functional and metabolic real-time imaging combined with iPDT offers a real benefit [78]. For iPDT guided by real-time imaging, nanoparticles were functionalized, consisting of a surface-localized tumor vasculature targeting neuropilin-1 (NRP-1) peptide (ligand) and encapsulated photosensitizer and magnetic resonance imaging (MRI) contrast agents. They were evaluated for their ability to produce $^1O_2$, to target NRP-1 and to confer photosensitivity. MRI-guided implantation of the optical fiber was performed prior to iPDT. The combination of non-invasive positron emission tomography with CT and magnetic resonance spectroscopy, allowed a therapeutic monitoring. A judicious choice of treatment regimens could possibly then maximize the outcome of iPDT.

Other studies focused on the use of metal-based nanoparticles to concomitantly perform PDT and a treatment-guided by imaging (for a review see [79]). Wang et al. used a titanium dioxide-based nanoparticles for combination of surgical resection and local PDT in glioma-bearing mice [80]. Interestingly, these biocompatible nanoparticles can be photocatalytically activated using UVA [81,82]. Gold nanoparticles are good candidates for efficient drug delivery as they can be easily functionalized (excellent surface chemistries and tunable size). Dixit et al. developed a multifunctionalized nanoparticle by targeting tumor cells in order to improve photosensitizer selectivity and perform intraoperative PDT after fluorescence-guided resection [83]. Epidermal growth factor and transferrin receptors are overexpressed in brain tumors. The dual-targeted gold nanoparticle consisting of epidermal growth factor (for tumor cell targeting) and transferrin (for cross blood-brain barrier) peptides loaded with a photosensitizer

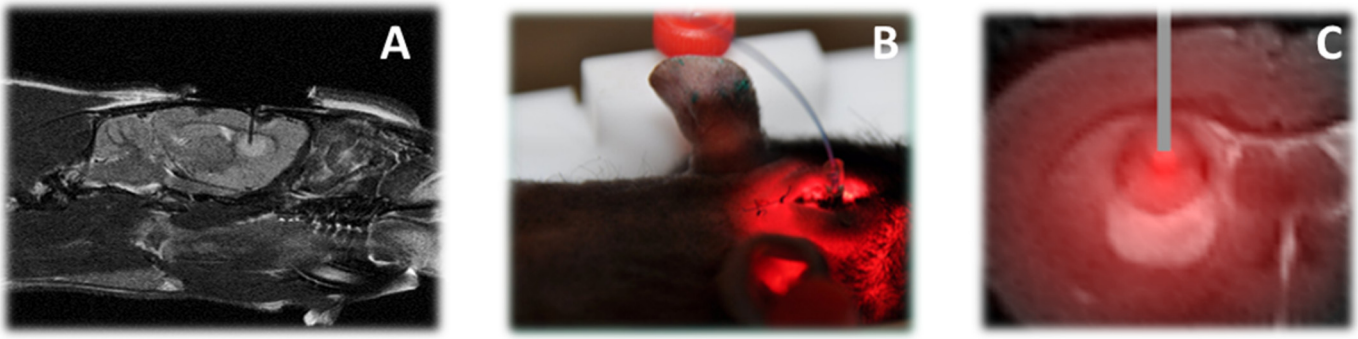

Fig. 4. A. Proton-weighted images (TR/TE: 5000/33 ms, NEX: 2, FOV: 4 × 4 cm, matrix: 256 × 256, SI: 1 mm) showing the fiber insertion in sagittal plane. B. A skull anchor was patented in order to control the positioning of the optical fiber into the brain tissue (WO/2012/176050 - CRANIAL ANCHOR). C. MRI analysis (T2 weighted images in coronal) after intravenous injection of AGuIX-porphyrin nanoparticles into rats with intracranial GBM and an illustrative implantation of the fiber positioning into the tumor tissue.

(phthalocyanine for PDT effect). Authors showed, in a mice bearing orthotopic U87 glioma, that nanoparticles with two targeting moieties increased accumulation of drug into tumor regions in contrast to nanoparticle with one targeting due to synergistic endocytosis mechanism of the ligands on the same drug delivery agent.

For unresectable tumors, iPDT may be with several optical fibers delivering light. Noninvasive imaging of small animals has developed in this context. Technical improvements today make it possible to quickly access extremely precise data with different levels of information: morphological, functional, and molecular. The great advantage of techniques non-invasive imaging is the possibility of integrating a temporal component into the characterization of a biological response by dynamically following its evolution *in vivo* (longitudinal studies). Contribution of nanomedicine coupling contrast agents allows non-invasive imaging to provide valuable assistance in the management of cancers real-time monitoring of the biodistribution of the drug and post-treatment therapeutic response. In the context using iPDT applied to GBM, MRI is a good candidate. To validate iPDT guided by MRI for GBM, a skull anchor was patented in order to control the positioning of the optical fiber into the brain (Fig. 4) [78; WO/2012/176050 - CRANIAL ANCHOR].

Early indicators of PDT efficacy and tumor progression remain essential for characterizing photo induced effects. Toussaint et al. showed that spectroscopy and diffusion magnetic resonance imaging monitoring can predict the tumor response after iPDT [84]. Authors used a multifunctional nanoparticles based on AGuIX® design (containing gadolinium for MRI) and conjugated with a porphyrin as photosensitizer. Apparent diffusion coefficient (ADC) values and the level of expression of choline, myo-inositol and lipids (Fig. 5) reported on the effect of iPDT on GBM by providing early non-invasive indicators of treatment efficacy.

Vascular effect plays a major role in the destruction of GBM by PDT. Anti-vascular PDT appears promising to improve tumor eradication. A selective accumulation of the photosensitizer into the tumor neovasculature favors this effect and therefore the photodynamic efficiency. Many studies using metal-based nanoparticles were suggested to improve this anti-vascular effect for iPDT-guided by MRI. Reddy et al. described the use of a multifunctional polymeric nanoparticle comprising a tumor-selective vascular homing peptide covalently conjugated to photosensitizer (photofrin) and imaging agent (iron oxide). Intravenous administration into in glioma-bearing rats provided an excellent tumor contrast enhancement [85]. Bechet et al. [78] used a gadolinium oxide-based core as a contrast agent for MRI at the periphery of a polysiloxane hybrid shell carrying the photosensitizer (chlorin) and a hydrophilic polymer to limit hepatosplenic recognition. A tumor vasculature targeting NRP-1 peptide (ATWLPPR) was coupled on certain polyethylene glycol chains. Real-time MRI analysis in orthotopic glioma model (Fig. 4) revealed the ability of the targeting peptide to confer specific intratumoral retention of the multifunctional nanoparticles. After intra-venous injection of peptide-targeted nanoplatforms, the positive contrast enhancement of the tumor by MRI allowed to visualize the proliferating part of the tumor tissue compared to un-conjugated nanoparticles. Multifunctional nanoparticles based on AGuIX® structure allowing a visualization of the tumor by MRI, were also conjugated with a new homing KDKPPR peptide targeting NRP-1 overexpressed by angiogenic endothelial cells and a porphyrin as photosensitizer to induce the photodynamic effect. The tumor selectivity of the nanoparticles compared to the healthy brain parenchyma was validated by MRI analysis. The selectivity for the tumor vascular endothelium of KDKPPR peptide *versus* a scramble peptide-functionalized nanoparticles was demonstrated using a nude mouse model with dorsal skinfold chamber, validating this vascular targeting strategy and the interest for a vascular targeted PDT with these multifunctional nanoparticles [86].

5.3. Near-infrared light-activated upconversion metal-based nanoparticle for PDT and imaging

To overcome the limited tissue penetration in traditional PDT and increase the ability to target glioma, Tang et al. developed a novel near-infrared light-activated upconversion nanoparticles functionalized with a photosensitizer (chlorin e6), a chelating agent, and a cyclic RGD peptide to target glioma tumor [87]. *In vivo* study in mice bearing subcutaneous U87 tumors showed that the newly developed near-infrared light-activated upconversion nanoparticle was a promising multifunctional cancer therapy modality because of the efficient tumor growth inhibition and good T1-weighted MRI imaging capability. Another study proposed to combine photodynamic and photothermal therapies using an Ytterbium-based up-conversion nanoparticle functionalized with a photosensitizer (mTHPC: 5,10,15,20-tetrakis(3-hydroxyphenyl) chlorin), a near-infrared fluorescence dye (IR-780) and angiopep-2 [88]. Angiopep-2 can trigger transcytosis and cross the blood-brain barrier recognizing low-density lipoprotein related protein-1 (LRP-1) expressed by endothelial cells. The biodistribution studies showed an enhanced accumulation of nanoparticle functionalized with angiopep-2 at the tumor site and the photoactivated dual therapies caused extensive apoptosis and necrosis.

Tang et al. described the interest of an iron oxide-based nanoparticle for a magnetic targeting combined with a chemotherapeutic agent doxorubicin and chlorin e6 for a photodynamic effect [89]. Authors showed that the magnetic nanoplatform could be guided by a specific magnetic field (0.5 T magnetic field on the tumor site) In subcutaneous U87 tumor bearing nude mice, the magnetic active targeting effect of the nanoplatform to the tumor site was obtained with relatively high doxorubicin and chlorin e6 concentrations, greatly improving the synergistic PDT/chemotherapy effect.

To conclude this section, we can suggest that to knock down the biotechnological barriers limiting the effectiveness of radiotherapy (curative X-ray dose to the tumor tissue without increasing it in healthy

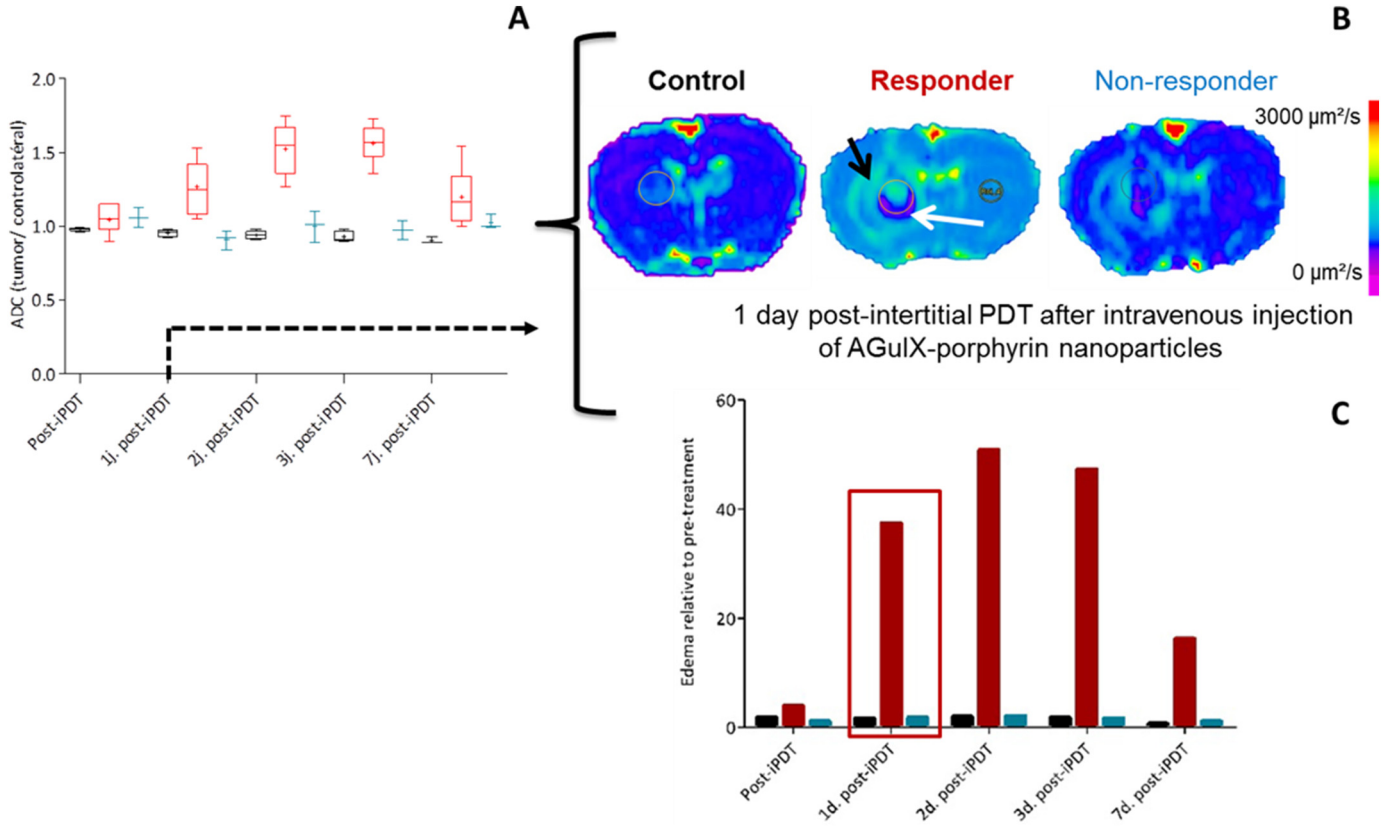

Fig. 5. From one day post-iPDT, diffusion weighted imaging allowed to identify promising markers such as the apparent diffusion coefficient (ADC) values (A). Apparent diffusion coefficient values of the tumor region (B) demonstrated statistically significant differences between the control, non-responder and responder groups, revealing a significantly higher frequency of high ADC values in the responder group, corresponding to a decreased cellularity into the tumor tissue due to the photodynamic effect. On ADC map, black arrows indicate a vasogenic edema and white arrows a cytotoxic edema. For the responder group (C), an extracellular edema and a cellular necrosis were events which coincided with an increase of the ADC values, adapted from [84].

tissue) and PDT (low penetration of light), a future proposal could be directed towards a breakthrough bimodal therapy guided by real-time computed tomography using biocompatible high-Z nanoparticles. This concept for GBM treatment could combine radiotherapy and PDT, two clinically proven modalities, while maintaining the main benefits of each. Only PDT can generate $^1O_2$, which is highly cytotoxic to tumor tissue, but unfortunately, the low penetration of light remains the limiting factor. To treat deep lesions without an invasive approach, X-ray could be used as an excitation source instead of light [90,91]. Thus, the light penetration problem through the tumor tissue will be overcome, and activation of the photosensitizer within tumor tissue will be performed by classical radiotherapy using ionizing radiation. Synergy between conventional radiotherapy and PDT will enable the use of classical X-ray doses associated with an improved efficiency. Moreover, X-ray computed tomography will provide high-resolution 3D structural details of tumor tissue without any invasion, which is highly beneficial for ionizing radiation location. Compared with the conventional computed tomography, imaging enhanced by high-Z nanoparticles could provide information about nanoparticle mapping into the tumor tissue, target delineation and precise the positioning for an accurate computed tomography imaging-guided radiotherapy of tumors. The future of PDT lies in the development of a single versatile nanoparticle which encompasses its applicability in both non-invasive imaging techniques as well as photodynamic efficiency.

6. Strategies using metal-based nanoparticles for blood-brain barrier crossing

The blood-brain barrier (BBB), which mainly consists of capillary endothelial cells and tight junctions, is a highly selective permeability barrier that separates the circulating blood from the extracellular fluid in central nervous system. However, BBB presents an essential obstacle to brain transports of therapeutics. In GBM, it is clearly disturbed [21] and nanoparticles can penetrate into the tumor tissue by EPR effect [92]. Nevertheless, at the early stage of brain tumors, the BBB remains intact. With tumor progression, BBB is still present in the infiltrative tumor region, which is preserve during the surgery and mainly responsible for the rapid recurrence of brain tumors. Thus conventional chemotherapeutics cannot be delivered to the brain effectively. Consequently, the development of nanomedicines, which can crossBBB, has the potential to improve the treatment of brain tumors. There have been major efforts with inorganic nanoparticles and the use of targeting moieties or blood-brain barrier breakdown caused by external stimulations (Fig. 6). In 2012, Yim et al. [93] showed a simple method to improve the penetration through the BBB of magnetic nanoparticles of MnFe2O4 by cross-linking serum albumin without disturbing the BBB. This approach could be easily applied to other metallic nanoparticles but for the moment, the selectivity for the tumor bed is not proven. Another interesting approach has been recently described *via* EPR effect in order to accumulate self-assembly golds nanoparticles into the tumor tissue using epidermal growth factor and a controlled release of chemotherapy drug (doxorubicin) by pH sensitive mechanism after cell endocytosis [94]. The targeting of specific receptors of BBB such as transferrin or insulin receptors allows a receptor mediated endocytosis, leading to an active transport mechanism of nanoparticles acrossthe BBB. Fang et al. [95] indeed showed that polydiacetylene nanocarriers containing SPIONs functionalized with lactoferin and curcumin could increase fourfold the amount of curcumin and suppress tumors in orthotopic brain-bearing rats. In the same way, Dixit et al. [96] demonstrated an accumulation of transferrin targeted gold nanoparticles loaded with photosensitizer into

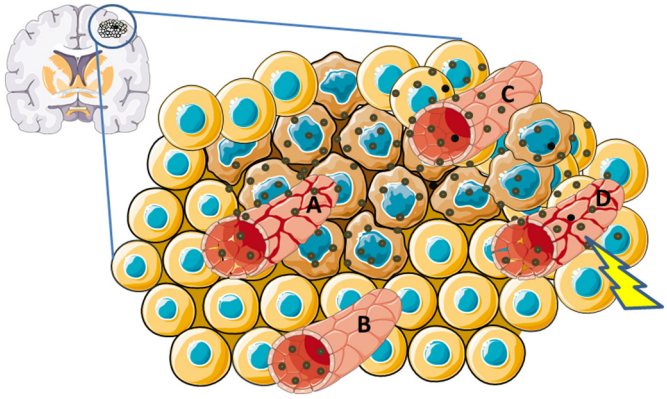

Fig. 6. Scheme representing the permeable blood tumor barrier in GBM tumor (A) which allows a passive diffusion and an accumulation of metallic nanoparticles by EPR effect in comparison to the selective BBB in healthy brain (B). Nanoparticles can be functionalized with specific ligands to cross the BBB (C), or focused external stimulations can also be suggested to transiently disturb the endothelial cell junctions of BBB in order to diffuse nanoparticles in the infiltrating zones (D).

brain tumor but without proof of *in vivo* photodynamic efficiency. External stimulation with physical disruption of blood-brain barrier BBB is another interesting approach notably because physical waves can be focused directly on the tumor or its periphery. X-ray can also permeabilize BBB [97], and recently Tamborini et al. [36] highlighted that chlorotoxin, targeting MMP-2 (matrix metalloproteinase-2) expressed by the tumor microenvironment and chloride channel-3 of glioma tumor cells, can be used to functionalize poly lactic-*co*-glycolic acid nanovector containing silver nanoparticles and combined with low dose X radiation improved the antitumor efficacy of these nanovectors. Ultrasound using microbubbles was shown also to locally and transiently open the blood-brain barrier to enhance the administration of therapeutic agents to brain tumor [98]. In 2013, Fan et al. [99] proved that SPIO-doxorubicin loaded microbubbles can cross it destabilized by focused ultrasound and accumulate in brain tumor when nanoparticles were attracted by magnet. Even if efforts have been made with metallic nanoparticles, few studies validated BBB crossing for *in vivo* GBM treatment (Table 1). Consequently, crossing BBB remains a major challenge to reach disseminated glioma cells and combined approaches such as nanoparticles for drug delivery and physical disturbance ofBBB.

7. General conclusion

Other the last decade, brain cancer research and medical practice have made good progress and now we are aiming for their early conclusion. In the field of high-grade brain tumor, the use of inorganic nanoparticles has been mainly fuelled by a lack of current solutions to many of the barriers that impede further progress. Nevertheless, clinical translation remains still very slow and sometimes laborious as very few related studies using metallic nanoparticles have reached clinical trials and fewer still for applications in the brain.

Metallic nanoparticles need to successfully overcome several major hurdles before being approved for a later commercialization. These include the development of a nanostructure with appropriate properties, an engineering of a reproducible manufacturing process, a favorable biodistribution profile, and a demonstration of efficacy in clinical trials. Additional regulatory and development considerations have to be taken into account when metal-based nanoparticles are submitted for approval by health authorities. The further development of nanomedicines applied to GBM treatment should also include a personalized medicine approach in order to identify subgroups that might benefit from these locoregional therapies, and will need to respond to the challenges posed by the emergence of metallic nanoparticles based on these new technologies.

For example, for precise temperature optimization, it will be of crucial relevance to use a correct experimental configuration, more importantly, to precisely monitor temperature during hyperthermia, which could positively impact heat dosimetry and clinical planning. It will be also of great importance to estimate the concentration of nanoparticles needed for providing desirable temperature elevation and the potentiality of controllable laser hyperthermia of deep tissue layers without damage to overlying tissue layers.

Owing to the multidisciplinary nature of these new medical strategies involving nanoparticle-based medical devices, it will be imperative to have frequent facilitations between scientists, engineers, clinicians and industrial innovators to share and discuss the opportunities, difficulties and challenges in the field.

Disclosure

The authors report no conflicts of interest in this work.

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Table 1
Summary of studies using metallic nanoparticles (NPs) for BBB crossing validated by *in vivo* brain tumor models.

NPs types	Size and formulation	Uptake mechanism to cross BBB	Target	Associated mechanisms of action	Brain tumor model	Reference
SPIO	1 μM, NPs encapsulated in Microbubbles	BBB disruption by ultrasound	Magnetic targeting	Doxorubicin release	C6 glioma cell grafted orthopically in rats	Fan et al. [99]
USPIO	100 nm, USPIO encapsulated in nanovehicles	Receptor-mediated Endocytosis	Transferrin receptor (lactoferin)	Curcumin release	RG2 cell grafted orthotopically in rats	Fang et al. [95]
Au NPs	600 nm, self-assembly of Au NPs	EPR effect	Epidermal Growth Factor Receptor of tumor cells	Doxorubicin release by Ph responsive mechanism	U87-MG cells xenografted orthotopically in nude mice	Feng et al. [94]
Ag NPs	114 nm; polymeric assembly of Ag NPs in PLGA	BBB disruption by irradiation	MMP-2/Chloride Chanel-3 (chlorotoxin)	NA	U87-MG cells xenografted orthotopically in nude mice	Matteoli et al. [36]

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