TOPICAL REVIEW — Magnetism, magnetic materials, and interdisciplinary research

Magnetic-mediated hyperthermia for cancer treatment: Research progress and clinical trials*

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(Received 9 August 2013)

Research progress and frontiers of magnetic-mediated hyperthermia (MMH) are presented, along with clinical trials in Germany, the US, Japan, and China. Special attention is focused on MMH mediated by magnetic nanoparticles, and multifunctional magnetic devices for cancer multimodality treatment are also introduced.

Keywords: magnetic-mediated hyperthermia, magnetic nanoparticles, alternative magnetic field, magnetic nanoparticle hyperthermia, thermochemotherapy

PACS: 81.07.–b, 75.75.–c, 87.50.ct **DOI:** 10.1088/1674-1056/22/10/108104

1. Cancer hyperthermia

Magnetic-mediated hyperthermia (MMH) is expected to be a new breakthrough for cancer treatment. Based on the working mechanism that heating up ferromagnetic biomaterials administered within the tumor site under alternative magnetic field (AMF), MMH can lead to a direct killing of local tumor tissue quickly with no interference to the normal tissue nearby. To meet the needs of clinical application, various kinds of magnetic mediators or agents have been developed, including millimeter-scaled thermoseeds or metallic stents for interstitial implant hyperthermia, micrometer-scaled particles for arterial embolization hyperthermia, and magnetic nanoparticles (MNPs) for intracellular hyperthermia. Recently, intensive and extensive investigations have been carried out with MMH, and some research findings have been successfully applied in oncology clinical.

Nowadays cancer has become a major public health problem and one of the leading causes of morbidity and mortality in the world. It was recently reported that one in three women and one in two men in the United States will develop cancer in his or her lifetime. In 2013, a total of 1660290 new cancer cases and 580350 cancer deaths are projected to occur in the United States.[1] Therefore, there is a need for a new approach in cancer treatment — more effective, more specific, and capable of increasing the patient's quality of life.

Hyperthermia has a long tradition in medicine as a treatment modality for various diseases. Inscriptions of the ancient Egyptians and texts from the peak of Greek civilization point out its importance.[2] Hippocrates of Kos (ca. 460 BC — ca. 370 BC), father of western medicine, also gave a famous comment on hyperthermia, in which he mentioned that "those diseases which medicines do not cure, the knife cures; those which the knife cannot cure, fire cures; and those which fire cannot cure, are to be reckoned wholly incurable." (Quae medicamenta non sanat; ferrum sanat. Quae ferrum non sanat; ignis sanat. Huae vero ignis non sanat; insanabilia reportari oportet.) Hippocrates evidently believed that some diseases could be cured by raising the patient's body temperature.

In modern medicine, the biological effectiveness of heat in treating cancer has been fully recognized although the mechanisms of heat cytotoxicity are yet unclear.[3–5] It may seem to be a relatively simple demand to heat up malignant tissues, but achieving selectively up to the desired temperature is far from a simple technical task. The potential role of hyperthermia in the management of human cancer will be difficult to assess until heating techniques and hyperthermia systems capable of delivering and monitoring safe, predictable and reproducible treatments are developed. It is generally acknowledged that the following criteria must be considered when the

*Project supported by the National Natural Science Foundation of China (Grant Nos. 81172182, 81172120, and 81041040), the 7th Singapore–China Cooperative Research Project Call between Agency of Science, Technology and Research (A*STAR), Singapore and the Ministry of Science and Technology (MOST), China (Grant No. 20113010006), and the National Key Technology Support Program (Grant No. 2012857818).

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hyperthermia approach is developed:

(i) Deepness — to achieve a deep energy delivery;

(ii) Focusing — to selectively focus on the malignant area only;

(iii) Reproducibility — to conduct the treatment in a reproducible way;

(iv) control — to have proper control of the process by standardizing the hyperthermia prescriptions (parameters of the treatment);

(v) Personalization — to tune the treatment *in-situ* to best fit the actual situation.[6]

2. Overview of magnetic-mediated hyperthermia (MMH)

2.1. Working mechanism and brief introduction to MMH

MMH, also called magnetic induction hyperthermia, is expected to be a new breakthrough in hyperthermia for cancer treatment. For the purpose of MMH, the tumor is infused or placed with magnetic agents. Upon exposure to an external alternating magnetic field (AMF), inductive heating is generated by the magnetic agents to form a high temperature zone (around 50 °C) at the tumor foci (Fig. 1). This process can lead to quick direct killing of the local tumor tissue, and in the meantime, activate the immune system to attack distant tumor sites, a phenomenon known as abscopal effect in cancer treatment.

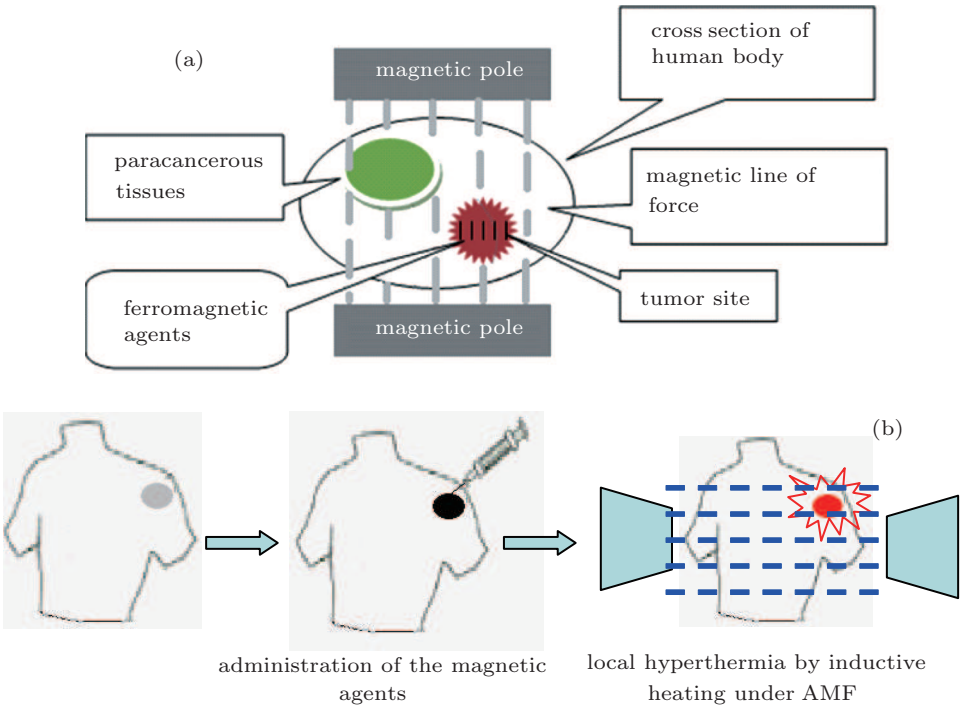


Fig. 1. Illustration of MMH: (a) schematic plot of MMH, (b) illustration of the MMH treatment process.

The concept of MMH was first proposed in the 1950s by Gilchrist, who demonstrated that magnetic particles could be deposited selectively at a tumor site and heat tumor tissue specifically when exposed to an AMF.[7] After thirty years of exploration, the world's first clinical trial with MMH by thermoseeds was carried out in Japan. Kida carried out clinical studies for brain cancer treatment and achieved very inspiring therapeutic success.[8–11] With the inspiration of that trial, MMH was further applied in clinical trials for prostate cancer and esophageal cancer. Results from prostate cancer treatment demonstrated that MMH by thermoseeds was feasible and could attain excellent tolerances in patients.[12–18] With the metallic stent as the magnetic agent, the results showed hyperthermia mediated by stent can improve the effectiveness of combination therapy, suppress local tumor growth, and enhance the quality of life over a long period.[19]

Currently, the explosive growth of nanotechnology has burst into challenging innovations in medicine, which is in the process of revolutionizing the MMH. Nanothermotherapies, which apply magnetic nanoparticles (MNPs) as heating agents, are a completely new approach for deep tissue hyperthermia application.[20–23] A rather homogenous temperature field can be achieved by the nano-scaled magnetic fluid. Moreover, it has been demonstrated that a 10-fold

higher uptake by cancerous cells than by the normal cells can be achieved through proper surface modification of the nanoparticles. Therefore "intracellular hyperthermia," which enables shifting the targeting of cancer treatment from tissue or organ level to the cellular level can be realized.[24] Taking all of the above together, the advantages of high selectivity and heating homogeneity can be expected in the use of either magnetic nanoparticle hyperthermia (MNH) or magnetic fluid hyperthermia (MFH). Currently, the world's first MNP based therapy against brain tumors, with the commercial name NanoTherm®therapy, is now under investigation in a phase-II study. Preliminary results show evidence of local effectiveness with only minor to moderate side effects. MFH, or NanoTherm®therapy, is one of the first applications of nanotechnology in medicine.[25] Besides the clinical trial, *in vitro* and animal experiments regarding MFH are widely carried out worldwide. Table 1 summarizes the major events associated with the development of MMH.

Table 1. Major events associated with the research development and clinical trials of MMH.

Time	Event
1957	The concept of MMH was initially described by Gilchrist *et al.*[7]
1959	MMH with magnetic particles was carried out on rabbits in which inguinal lymph modes were successfully targeted with heat.[165]
1976	The earliest report of AEH by applying a dog kidney model was published by Rand *et al.*[166]
1979	The concept of intracellular hyperthermia was first proposed by Gondon *et al.*[167]
1990	Kida reported the phase I clinical trial of MMH by thermoseeds for malignant gliomas in Japan.[8]
1992	Stea *et al*. completed the phase I clinical trials of MMH by thermoseed for malignant gliomas in US.[10]
1993	Jordan *et al*. published the first fundamental work describing the real potential of magnetic fluids for hyperthermia.[100]
2004	Deger *et al*. reported the phase I/II clinical trials of MMH by thermoseeds for prostate cancer in Germany.[16,17]
2003∼2005	MagForce Nanotechnology AG carried out the phase I clinical trials of MNH in Germany.[135–137]
2005	MagForce Nanotechnology AG initiated the phase II clinical trials of MNH in Germany.[138]
2006	Akiyama *et al.* carried out clinical trials of MSH in Japan.[19]
2008	The concept of Nanothermotherapy was first proposed by Gazeau F *et al*.[168]
2009	The first report of post-mortem neuropathological findings of GBM patients undergone MNH was reported.[169]
2009	Ethical discussion on MFH for brain cancer was published.[25]
2009	Phase I clinical trials of MMH by thermoseeds was carried out in China.
2011	Efficacy and safety evaluation for MNH on recurrent GBM was reported.[138]
2013	MNH received approval from German Federal Institute for drug and medical devices (BfArm) to start the post-marketing study in GBM with NanoTherm®therapy.[170]

2.2. Categories of MMH

Compared with other traditional hyperthermia approaches, such as ultrasound, microwave, radiofrequency, etc., the unique advantage of MMH lies that it can deliver tumor-specific hyperthermia to elevate local temperature for effectively killing-off the tumor cells, while stimulating the body's active immunity as well. Since the inductive heating zone for cancer treatment is only within the tumor site, MMH can realize rather high temperature hyperthermia, not restricted to traditional hyperthermia temperatures around 43 °C, therefore greatly enhancing the therapeutic efficacy for tumors. According to the different administration pathways of the magnetic agents, MMH can be divided into four categories: arterial embolization hyperthermia (AEH), direct injection hyperthermia (DIH), intracellular hyperthermia (IH), and interstitial implant hyperthermia (IIH).[26] According to the scale of the magnetic agents, they can be divided as millimeter-scaled agents (ferromagnetic alloy thermoseed, metallic stents) micrometer-scaled agents (usually for the purpose of AEH) and magnetic nanoparticles (MNPs, or magnetic fluid). Figure 2 illustrates the types of agents and Table 2 summarizes the main features and clinical trials of MMH with magnetic agents of different scales.

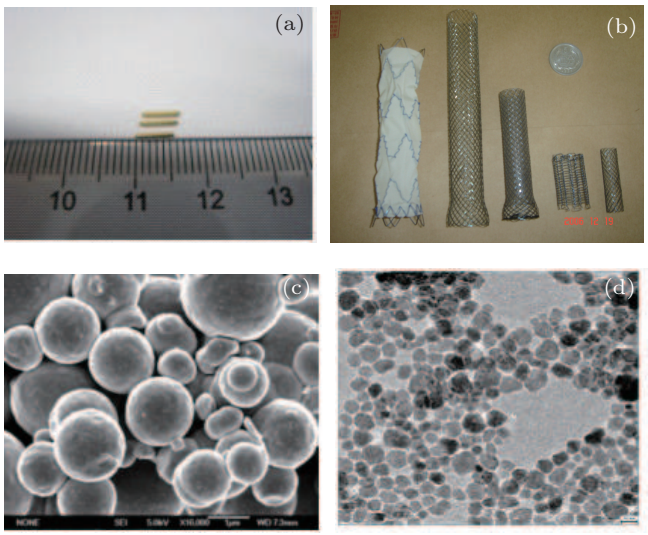


Fig. 2. Different types of magnetic agents: (a) alloy thermoseed for interstitial hyperthermia, (b) metallic stents for interventional hyperthermia, (c) micro-size carbonyl iron powder for AEH, (d) MNPs for intracellular hyperthermia.

Table 2. Magnetic agents of MMH cataloged by scale.

3 Scale of therapeutic agents	Technical title	Application	Components	Clinical trial
Millimeter	themoseed or stent	IIH or interventional hyperthermia	ferromagneticloy	phase I/II
Micrometer		AEH	magnetic particles coated with polymeric shell	
Nanometer	ferrofluid or magnetic fluid	IH and AEH	Fe_3O_4 or γ-Fe_2O_3	phase I/II

3. Research progress of MMH

3.1. IIH by thermoseeds and magnetic stent hyperthermia

3.1.1. IIH by thermoseeds

Though numerous studies carried out with various animal models have yielded convincing evidence in favor of hyperthermia as a primary or adjunctive cancer treatment in preclinical conditions, clinical acceptance of hyperthermia has been slow. Several factors may account for the seeming inconsistence; e.g. the present means of mapping and measuring the administered thermal dosage is considered inadequate and is priority one for further research. MMH by thermoseeds could be one solution to this problem, essentially by utilizing a low Curie point to achieve thermal self-regulation, thereby eliminating the costly and invasive thermometry now associated with hyperthermia. Lilly *et al.* developed self-regulating thermoseeds for IIH treatment of tumors.[27] The synthesized thermoseeds, composed of 70.4% nickel and 29.6% copper, possess a Curie point of 50 °C. An inductive heating profile indicates that the thermoseeds' rate of heat production drops sharply at temperatures above the Curie point when exposure to an AMF (90 kHz, 50 Oe, 1 Oe = 79.5775 $A{\cdot}m^{-1}$), demonstrating self-regulation of temperature during the treatment. Later, Rehman *et al.* carried out an *in situ* study for ferromagnetic self-regulating re-heatable thermoseeds implants for tissue ablation.[28] The palladium and cobalt temperature-self-regulating thermoseeds were designed to develop a maximum temperature of 70 °C. The seeds were placed in renal, hepatic, uterine, and pancreatic areas of 16 pigs. Results revealed that higher temperature ($>$ 50 °C) can be achieved in all tissues with properly aligned thermoseeds. Histological evaluation showed necrosis extended 2 mm beyond the periphery of the thermoseeds. The possible reason, as explained by the authors, may be the technical misalignment of the thermoseeds, as the authors attempted to treat more than one organ in each pig. Still, their results well support the proposition that properly aligned thermoseeds can create well-defined areas of necrosis with no skipped areas of viable tissue within the treated area. Moreover, as the seeds can be reactivated at any time, recurrent lesions within the same site can be treated repeatedly.

For the research work on the ferromagnetic thermoseeds, special attention has been paid to the thermal treatment effect on the heating characteristics, as it has been proved that treatment process plays a critical role in the inductive heating properties of the thermoseeds. Work by Ferguson revealed that recrystallization (including annealing times and temperatures) is crucial for altering the seeds' heating characteristics.[29] It is possible to increase the maximum heating temperature (Curie point) by increasing the annealing time and cooling time. Other factors, such as alloy composition and coating treatment also affect the heating property.

3.1.2. Magnetic stent hyperthermia

While the interstitial implant hyperthermia can be achieved by ferromagnetic alloy thermoseeds of rod shape in particular, any metallic medical device that can generate heat when subjected to AMF can be applied as a local "heat source" for cancer therapy, for instance, cylindrical metallic stents composed of alloy wire. Shoji *et al.* carried out some pioneering work on the feasibility of magnetic stent hyperthermia.[30] Furthermore, they carried out an *in vivo* investigation in the large intestine of Sprague–Dawley rats, as the bile duct of a rat is too narrow. The stent was then subjected to a magnetic field of 157 kHz. The results indicate that magnetic stent hyperthermia is feasible, as the temperature can be raised to 45 °C and the treatment is tolerable.

Our group also carried out a series research efforts on MSH for esophageal cancer treatment. We have demonstrated that the medical Ni–Ti stent possesses excellent inductive heating characteristics under AMF.[31–34] *In vivo* safety evaluation of MSH was carried out on pigs and our observation proved that a pig esophagus can actually endure higher temperature treatment without mucous hyperemia or tissue edema, indicating that MSH is safe. However, it is impossible or inconvenient to grow a tumor in a pig's esophagus, although humans and pigs share similar physiological indexes in many aspects. Effectiveness evaluation was performed on the rabbit esophageal tumor model and our results show that MSH can effectively inhibit tumor growth for the rabbit esophageal tumor model.

3.2. AEH for liver cancer

AEH is an experimental modality of hyperthermia that consists of selective arterial embolization of tumors with ferromagnetic particles followed by exposure to AMF to generate heating of the embolized particles and also the surrounding tissues.[35] AEH has shown promise as a method for local

cancer treatment with high temperatures, especially for liver tumors. It is well established that liver tumors derive virtually all their blood supply from the hepatic arterial system, while the normal hepatic parenchyma is supplied mostly by the portal venous system.[36]

3.2.1. AEH by microscaled magnetic particles

Moroz *et al.* from the University of Western Australian has conducted a series of *in vivo* investigations of AEH that consisted of arterially embolizing rabbit liver VX2 tumors and pig renal artery with ferromagnetic particles.[35–41] They found that AEH can target deep-seated, vascularized tissue in a large animal (pig) with therapeutic temperatures (> 42 °C), and the treatment is safe and well tolerated. They further confirmed that there is a linear relationship between heating rate and iron concentration within the liver. An *in vivo* study performed on the tumor model demonstrated that ferromagnetic particles can result in excellent targeting of liver tumors. For the comparison of tumor response to AEH and DIH, their findings indicate that AEH is more effective than DIH at moderately elevated temperatures. The explanation, as they suggested, may be that more widespread particle distribution can be achieved by transcatheter arterial embolization (TAE), which results in more extensive and complete treatment of the tumor.

The particles applied by Moroz consisted of MNPs (γ-Fe_2O_3, 100 nm) encapsulated with a polymer matrix to form 32-μm-diameter microparticles, as it had been argued by Jones that mediator particles for AEH should be micron-sized to ensure that they are trapped in the capillary bed surrounding the tumor rather than passing through to the venous circulation.[42] Under such consideration, Li *et al.* carried out a series of research work on fabricating MNPs encapsulated in silica microspheres for AEH. The sol–gel process was employed with tetramethoxysilane (TMOS) in water-in-oil emulsion. By applying the protocol, α-Fe-encapsulating silica microspheres were prepared. The obtained microspheres have a saturation magnetization (M_s) up to 21 emu·g^{-1} and a coercive force (H_c) of 133 Oe. The magnetic microspheres demonstrated an ideal inductive heating property in an AMF of 300 Oe and 100 kHz.[43,44]

Recently, we evaluated the feasibility of carbonyl iron powder (CIP) as a novel mediator for AEH.[45,46] ICP (trade name, Ferronyl®, ISP Pharmaceuticals) has been approved by FDA as a dietary iron supplement for oral administration, due to its low toxicity and excellent bioavailability. It is elemental iron with high iron content and highly resistant to oxidation. The typical average particle size is about several microns, which enables its further application as a mediator for AEH. A cytotoxicity study demonstrated that CIP has good biocompatibility. Heating curves, both *in vitro* and *in vivo*, reveal that CIP possesses ideal inductive heating characteristics under AMF. AEH mediated by CIP/Lipiodol can effectively inhibit tumor growth on the rabbit VX2 liver tumor modal. Our findings suggest that CIP is a very promising candidate as mediator of AEH for clinical application.

3.2.2. AEH by MNPs

Although micro-sized magnetic particles may have advantages over the MNPs in accumulating within the tumor site, as suggested by Jones,[42] with their excellent inductive heating property and size-controllable synthesis protocols, MNPs provide extra feasibility for mediating AEH. Shigeyuki *et al.* reported a feasibility study of AEH by nano-sized magnetic particles (ferucarbotran) in rabbits.[47] The ferucarbotran they employed as the AEH agent was purchased from Resovist, Shering, German. It is a dextran magnetite complex which is now widely used in daily clinical practice as an MRI contrast agent. It is especially noteworthy that the permissible dose of ferucarbotran in humans had already been established. Their findings demonstrated that in the heating rates of the kidney, ferucarbotran could lead to a significant temperature increase. In the AEH group, tumors could be selectively heated.

Yu *et al.*[48] conducted combination therapy for arterial embolization hyperthermia (AEH) with arsenic trioxide (As_2O_3) nanoparticles (ATONs) — a novel treatment for solid malignancies. This study was performed to evaluate the feasibility and therapeutic effect of AEH with As_2O_3 nanoparticles in a rabbit liver cancer model. Their results demonstrate that ATON-based AEH is a safe and effective treatment that can be targeted at liver tumors using the dual effects of hyperthermia and chemotherapy. This therapy can delay tumor growth and notably inhibit tumor angiogenesis.

3.3. Magnetic hyperthermia by MNPs

The rapid advances in nanotechnology have improved the ability to design and manufacture the biomaterials for the purpose of specific biomedical applications. In recent years, considerable efforts have been made to develop MNPs.[49,50] Possessing appropriate physicochemistry and tailored surface properties, MNPs have been extensively investigated for various applications such as drug delivery, hyperthermia magnetic resonance imaging (MRI), tissue engineering and repair, biosensing, biochemical separations, and bioanalysis.[51–54]

3.3.1. Synthesis and surface coating of MNPs

In MMH, SPIONs include γ-Fe_2O_3or Fe_3O_4 particles with a core size of < 10 nm and an organic or inorganic coating. The SPIONs can be controllably synthesized by various chemical routes, including classic synthesis by precipitation, high-temperature reactions, reactions in steric environments, sol–gel reactions, decomposition of organometallic precursors, polyol methods, etc. Excellent reviews can be found that

address the synthesis protocols for SPIONs.[49,50] The simplest, cheapest, and most environmentally-friendly procedure by far is based on a co-precipitation method, which involves the simultaneous precipitation of Fe_2^+ and Fe_3^+ in a basic aqueous media. SPIONs synthesized in this way are hydrophilic and no further phase transition is needed.

Since the as-synthesized SPIONs in colloidal form (known as ferrofluid or MF) have a large surface to volume ratio, they are easy to aggregate to form large clusters. Therefore, surface coating or modification is required to improve the properties of the MF, such as stability and dispersity, to deter aggregation in either a biological medium or a magnetic field. Numerous review papers have been published addressed the surface coating of MNPs and either inorganic or organic materials can act as a stabilizer for SPIONs.[55–65] Among inorganic materials, silica,[66–68] gold[69–71] or gadolinium[72,73] are the commonly applied coating materials. These coatings not only provide stability to the nanoparticles in solution, but also help to bind various biological ligands to the SPION surface. Numerous review papers address the surface coating of MNPs, and so far, approaches have been developed to coat SPIONs with polymeric materials, including *in situ* coating,[63,64], post synthesis coatings,[76–81] deposition methods[82,83] as well *in situ* polymerization process.[84] The polymers employed in the surface coating mainly include polyethylene glycol (PEG), dextran, aminosilane, chitosan, etc.[85–90]

3.3.2. Research progress in MNP-mediated hyperthermia

Beyond SPION synthesis and surface modification, in the last 20 years, a full spectrum of MNH-related cancer treatment research has been systematically carried out — modeling MNP distribution and heat dissipation, or evaluating nanotoxicity, *in vitro* cytotoxicity, *in vivo* antitumoral effects, etc.[21,90–99] A research group led by Jordan carried out pioneering and comprehensive work on MNH.[100–104] They compared the endocytosis of dextran- or aminosilane-coated Fe_3O_4 MNPs with human malignant and normal cells *in vitro*. Their observation confirmed that clonogenic cell survival was 3-fold lower after MNH versus water-bath hyperthermia. By comparing the results, they also concluded that dextran-coated MNPs were not suitable for MNH approaches. One of their *in vivo* studies, conducted on 120 male Fisher rats bearing RG-2 glioblastoma, revealed that MNH by means of aminosilane-coated MNPs prolonged patient survival 4.5-fold over control patients, while dextran-coated particles did not show any advantage.[104] They also observed that intratumoral deposition of the silane-coated particles was very stable, so repeatable treatment without repeated MNPs infusion is guaranteed. However, research reported by Wada *et al.*, who also employed dextran-coated MNPs demonstrated that after MNPs were injected into one side of a golden hamster's tongue, regulating the intensity under an AMF could maintain the local tissue temperature at 43 °C to 45 °C.[105] Subsequently, Wada injected MNPs into DMBA-induced tongue cancer in a golden hamster. Under an AMF of 500 kHz, tongue cancer could be effectively controlled. Beyond that, work with Fe_3O_4 MNPs coated with polysaccharides, oleic acid, proteins, silica, carbon, gold, chitosan, and biocompatible polymers has been reported recently.[106–113] Our research group also conducted systematic investigation on SPION-mediated hyperthermia, and simulated *in vivo* tests were performed on tumor models of liver cancer, malignant glioma, breast cancer, pancreatic cancer, lung cancer, malignant melanoma, and esophageal cancer.[113–121] Besides Fe_3O_4 magnetite nanoparticles, maghemite nanoparticles (γ-Fe_2O_3), another type of SPION, also have been applied in MNH as an effective mediator.[122,123] All the observations suggest that SPIONs mediated hyperthermia is an effective, safe and minimally invasive treatment.

Another approach that has drawn much attention in recent years is the conjugation of monoclonal antibodies or cell-specific ligands with MNPs for the purpose of targeted hyperthermia. It has been demonstrated that nanoparticles coated with dextran modulated by anti-HER-2/neu monoclonal antibodies have a specific cell-conjugating capacity and excellent temperature-raising effect on co-cultured breast cancer cells.[124–127] By conjugating the epidermal growth factor (EGF) with MNPs, the MNPs were observed to effectively target over-expressed epidermal growth factor receptor (EGFR) cells, resulting in a significant (up to 99.9%) reduction in both cell viability and clonogenic cell survival in a thermal heat dose-dependent manner.[128,129] Monoclonal-antibodies or ligands, such as chimeric L6 (ChL6), folic acid, etc., were also selected for active targeting studies to modify magnetic nanoparticles[130–132] In all these instances, the capability of magnetic nanoparticles to target and conjugate to specific tissues and tumor cells was confirmed.

In addition to SPIONs, much attention has been given to the synthesis of MNPs with novel structures that have a high specific adsorption rate (SAR). SAR, also called specific power loss (SLP), is widely applied to quantify the heating capacity of MNPs and can be calculated based on Eq. (1)

$$\mathrm{SAR} = C(\Delta T/\Delta t)(1/m), \tag{1}$$

where C represents the sample-specific heat capacity (in unit $\mathrm{J/g^{-1}\cdot K^{-1}}$, both the nanoparticle material and the dispersion medium are considered), $(\Delta T/\Delta t)$ is the increase in temperature with time and m is the amount of magnetic material used in the experiment. In any case, it is desirable to realize the temperature enhancement needed for any given application with as few MNPs as possible. This means that the heat power generated per particle unit mass should be as high as possible.

Recently, taking advantage of the exchange coupling between a magnetically hard core and magnetically soft shell to tune the magnetic properties of the MNPs, Lee *et al.* demonstrated that the core-shell structured MNPs have SAR values that are an order of magnitude larger than conventional SPIONs.[132] High SAR values were also reported for cube-shaped water-soluble iron-oxide nanocubes (IONCs) prepared by Guardia in a size range between 13 nm and 40 nm.[133] Among the different sizes tested, IONCs with an average diameter of 19 ± 3 nm had significant SAR values in clinical conditions and reached SAR values up to 2452 W/gFe at 520 kHz and 29 kA·m^{-1}, which is one of the highest values so far reported for IONCs. *In vitro* trials carried out on KB cancer cells treated with IONCs of 19 nm have shown efficient hyperthermia performance, with cell mortality of about 50% recorded when an equilibrium temperature of 43 °C was reached after 1 h of treatment

However, though compared with the novel magnetic nanostructured devices with high SAR values, SPIONs exhibit only a medium heating efficiency with minimal control of *in vivo* temperature evolution during the treatment, surprisingly, both experimental and commercially available MNPs for hyperthermia normally consist of SPION cores. This is because although SAR value plays a paramount role in choosing the mediator for hyperthermia, other considerations should still be met for biomedical applications, such as biocompatibility, non-toxicity, ability to escape from the mononuclear phagocyte system, as well as low protein adsorption, etc. SPIONs can simultaneously satisfy many biomedical needs, and for this reason they are widely applied in MRI, drug delivery, magnetic hyperthermia, and tissue repair without any detectable cytotoxicity at the applied dosage.

4. Clinical applications of MMH

4.1. Clinical trials of MMH by thermoseeds

The world's first clinical trial of MMH by thermoseeds was carried out in Japan. Kida *et al.* reported the first clinical experience of interstitial hyperthermia of malignant brain tumors by ferromagnetic thermoseeds in 1990, with a Curie point of 68 °C.[8,9] Though the applicability of the results is still tentative, the overall response rate was an encouraging 34.8%. Degeneration of tumor cells, hemorrhage, vascular stasis, and thrombosis were found adjacent to the necrosis. Two years after that, Stea *et al.* completed a phase I study of interstitial thermoradiotherapy for high-grade supratentorial gliomas.[10,11] The main purpose of this trial was to test the feasibility and toxicity of MMH by thermoseeds. Among the 28 patients, 22 were treated at the time of their initial diagnosis with a course of external beam radiotherapy followed by an interstitial implant with Ir-192. Six patients with recurrent tumors received only the interstitial implant. A 60-minute hyperthermia treatment was given just before and right after completion of brachytherapy via the same catheter. Hyperthermia was generally well tolerated. The preliminary survival analysis showed that 16 of the 28 patients have already died, with a median survival of 20.6 months from diagnosis. The authors concluded that interstitial hyperthermia of brain tumors with ferromagnetic implants is feasible and carries significant but acceptable morbidity, given the extremely poor prognosis of this patient population. Subsequently, they used hyperthermia therapy with radiotherapy to compare their efficacy together with that of radiotherapy alone. Results showed that for around 50% of 25 patients with primary tumors, therapy was efficacious, and that MMH was one of the factors closely correlated with the patient survival period ($P < 0.05$).

With the inspiring results from the clinical trials for malignant brain cancer, clinical trials of MMH by thermoseeds was also carried out for the targeted treatment of prostate cancer. In 2000, Tucker *et al.* carried out ablation of prostate cancer by MMH with thermoseeds.[12–15] They applied thermoseeds with Curie points of 55 °C, 60 °C, and 70 °C, respectively. They observed that arrays of 70 °C seeds placed within 1 cm of each other caused consistent necrosis between the seeds. As the temperature at the edge of the array dropped off quickly, they suggested that thermoseeds can be placed within 2 mm of the capsule even posteriorly near the rectum, indicating a rather safe treatment. Based on their findings, they concluded that arrays of high-temperature thermoseeds (70 °C) can be employed for tissue ablation, while lower-temperature arrays could be used to produce hyperthermia in order to achieve synergism with adjuvant radiation therapy. As the treatment process is easy and convenient to operate, they further proposed that the technique of MMH is applicable in an outpatient setting. The level of prostate-specific antibodies markedly increased in the subjects. Eight weeks after the treatment, antibody levels were significantly lowered as compared with pre-treatment levels.

Recently, based on a variety of experimental and phase I clinical data, which together have proven the synergistic effects of MMH to radiotherapy, Deger *et al.*, from Humboldt University in Germany, reported on a phase II trial to determine the feasibility, acute toxicity, and efficacy of thermoradiotherapy for prostate cancer. The clinical trial was conducted between 1997 and 2000 on 57 patients with localized prostate cancer. During the treatment, intraprostatic temperatures were between 42 °C and 46 °C with no major side effects associated.[16,17] They carried out median follow-ups up to 36 months. The phase II clinical trial strongly suggested that MMH by means of thermoseed is feasible, well tolerated and leads to a steep decrease of PSA values. Combining MMH with conformal radiotherapy may be an exciting innovative treatment option for prostate cancer.

From 2010, our research group has been pioneering the clinical trial of thermoseed-based MMH. We obtained approval from SFDA, and patients with soft tissue sarcoma were received such treatment. Gold-coated nickel–copper alloy thermoseeds (Fig. 2) with Curie point of 80 °C were applied. So far, the phase I clinical trials have been successfully finished and the phase II trial is ongoing. Results from the clinical trials strongly demonstrated that MMH by thermoseeds is effective, safe, minimally invasive, and quite tolerable.

4.2. Clinical trials of MSH

A clinical trial of MSH was carried out in Japan. Akiyama studied the feasibility of employing a metal esophageal stent for magnetic induction hyperthermia.[19] Eighteen T3/T4 esophageal cancer patients with dysphagia were selected for this pilot clinical trial. Stages II, III, and IV involved 1, 10, and, 7 cases respectively. Thirteen patients received MMH with adjunctive chemotherapy while 5 received MMH with adjunctive radiochemotherapy. Throughout the entire course of therapy, patients displayed excellent tolerance. During hyperthermia, patients felt only mild warmth at the physical point of therapy. No complications associated with this hyperthermia were observed. In comparison with traditional canal hyperthermia, the reticular stent increased the heat exposure area of tumors. MMH raised the temperature during tumor therapy so as to boost the curative effect. Table 3 summarizes the clinical trials of MMH by thermoseeds.

Table 3. Clinical trials of MMH by thermoseeds.

Institution	Cancer type	Number of patients enrolled	Ferromagnetic alloy
Nagoya University, School of Medicine; Komaki City Hospital, Japan[8,9]	magligant gliomas	24	Fe–Pt
University Iowa Hospital, US[12–15]	prostate	20	Co–Pa
Hunboldt University, Germany [16,17]	prostate	57	Co–Pa
University of California, Comprehensive Cancer Center, US[18]	prostate	14	Co–Pa
Department of Radiation Oncology, University of Arizona, US[10,11]	supratenorial gliomas	28	
Nogaya University, School of Medicine, Japan[19]	esophageal cancer	18	Fe–Pt metallic stent

4.3. Clinical Trials of MNH

The persistent efforts and inspiring results of MNH led to the world's first phase I trial on 14 patients with glioblastoma multiforme (GBM) at the Charité–University Medicine Berlin from March 2003 to January 2005.[136,137] Note that the quick start of the clinical studies was due to the approval of the MNPs as part of a medical device but not as a drug, thus shortening the ponderous approval process for drugs.[25] A 3D image-guided intratumoral injection of aminosilane-coated iron oxide nanoparticles was conducted under general anesthesia and distribution of MNPs throughout recurrent or nonresected primary tumors was confirmed. During the hyperthermia process, neither immobilization nor anesthesia of the patient was required and the whole treatment took only about 2 hours. The median maximum intratumoral temperature was kept around 44.6 °C. The patients received six treatments (two per week). MMH was tolerated well by all patients with minor or no side effects, such as headache, nausea, vomiting, allergic reactions, or neurological deficits. No bleeding, swelling of the brain, or rise in intracranial pressure occurred during or after the treatment. Signs of local tumor control were observed. A median survival of 14.5 months seems promising with the trials. This phase I trial has shown the feasibility, tolerability, and efficacy of MNH. Except for GBM, the phase I clinical trials of MNH were carried out on prostate carcinomas and other entities.

With the success of the phase I study, a phase II study was subsequently started in January 2005.[138] It is still in progress to evaluate the efficacy of the treatment on 65 patients suffering from recurrences of glioblastoma multiforme. Another clinical study conducted with 22 patients with nonresectable and heavily pretreated recurrences of different other tumor entities having undergone radiation therapy and/or chemotherapy. All the trials show that MNH can be applied without complications.

4.4. Clinical trials of AEH

Compared with clinical trials of MMH with thermoseeds or MNH, systemic clinical trials have not been initiated for AEH. Jordan *et al.* reported their clinical experience to prove the feasibility of selective arterial infusion of SPIONs in patients with hepatocellular carcinoma (HCC).[139] Thirteen patients with HCC who underwent modified transarterial chemoembolization (TACE) were enrolled in this study. Six received concurrent infusion of ferucarbotran (Resovist, Schering, Berlin, Germany) in tumor-feeding arteries, and another six received an infusion of SPIONs produced by MagForce Nanotechnologies, Berlin, Germany. The iron content of both dispersions was 3.92 mg. It confirmed that selective arterial infusion of both SPIONs results in a significant decrease of intratumoral signal intensity on T1-weighted se-

quences ($P < 0.0001$), which was greater after MagForce infusion than after Resovist ($P = 0.002$). Only minimal amounts of dispersed particles were found in adjacent normal liver parenchyma. No change in intratumoral signal intensity was noted when ferromagnetic particles were omitted. Results from this clinical experience prove that TACE with a selective arterial infusion of SPIONs can be used for precise tumor targeting in patients with HCC, for which MagForce appears to be superior to Resovist.

5. Multifunctional magnetic devices for cancer multimodality treatment

While much research has been carried out with MMH and has also led to clinical success, in clinical oncology, hyperthermia alone is probably most useful for palliative treatment. Since heat has been demonstrated experimentally to sensitize cells to ionizing radiation and several chemotherapeutic agents, hyperthermia combined with either radiation or systemic chemotherapy has rapidly become a clinical reality as a form of treatment for malignant disease.

5.1. Multifunctional magnetic device for thermoradiotherapy

5.1.1. Heat-induced radiosensitization

The enhancement of cellular radiosensitivity by additional heat treatment is a well-documented phenomenon.[140] In general, the maximum cytotoxic effect can be observed when radiation is applied simultaneously with heat. For several decades, evaluation of the effects of heat on radiation response has been one of the most active research areas, with the purpose of an improved understanding of the mechanisms by which heat potentiates radiation-induced cell killing.

As it is conclusively recognized that for cell killing by ionizing radiation, radiation to the cell nucleus will mainly determine the extent of the treatment effect, many investigators have studied how heat will interact with radiation damage of the chromosomal level, and strong evidence has proved that heat can increase the primary DNA damage or inhibit the repair of such damage.[141–143] It has been demonstrated that heat treatment after irradiation can remarkably increase the number of chromosome aberrations or of micronuclei. These observations demonstrate that the mechanism of radiosensitization by heat must interfere with processes at the chromosomal level and enhance irreparable chromosome damage in comparison to irradiation alone. However, DNA may not be the only or the primary target of IR, and meanwhile, heat can affect all aspects of cellular metabolism. Much research output has confirmed that the mechanisms of radiosensitization are complex and not completely understood. For instance, Pawlik *et al.* demonstrated that hyperthermia can induce cytoskeletal alterations and mitotic catastrophe in p53-deficient H1299 lung cancer cells.[144]

5.1.2. Radiothermotherapy mediated by thermobrachytherapy seed

Recently, Gautam *et al.* developed a novel thermobrachytherapy seed with a ferromagnetic core for treatment of solid tumors.[145] The proposed seed is based on the BEST Medical, Inc., Seed Model 2301-I,[124] wherein a tungsten marker core and an air gap are replaced with ferromagnetic material. The ferromagnetic core could produce heat when subjected to AMF and effectively shut off after reaching the Curie temperature of the ferromagnetic material, thus realizing self-regulation of temperature. For the thermal characteristics, the authors studied a model consisting of 16 seeds placed in the central region of a cylindrical water phantom. The thermal modeling results show that the temperature of the thermoseed surface rises rapidly and stays constant around the Curie point of the ferromagnetic material. The amount of heat produced by the ferromagnetic core is sufficient to raise the temperature of the surrounding phantom to the therapeutic range. The phantom volume reaching the therapeutic temperature range increases with any increase in frequency or magnetic field strength. Although no *in vivo* investigation was carried out, the proposed combination seed model has potential for implementation of concurrent brachytherapy and hyperthermia by a single multifunctional device.

5.2. Multifunctional magnetic devices for thermochemotherapy

5.2.1. Thermochemotherapy: Thermal enhancement of drug cytotoxicity

As hyperthermia can effectively enhance the cytotoxicity of various antineoplastic agents (thermal chemosensitization), in several phase-III clinical trials, an improvement of both local control and survival rates have been demonstrated by adding local/regional hyperthermia to chemotherapy for patients with locally advanced or recurrent superficial ad pelvic tumors.[146–148] Additional application of selected chemotherapeutic drugs has been shown to enhance the inhibition of clonogenic cell growth at elevated temperatures both *in vitro* and in animal experiments. Thermal enhancement of drug cytotoxicity is accompanied by cellular death and necrosis without increasing its oncogenic potential.[149] It also has been recognized that mechanisms for the thermal enhancement include increased rate constants of alkylation, increased drug uptake, inhibition of repair of drug-induced lethal or sub-lethal damage, etc. Generally, as supported by a wealth of biomedical and molecular biological data, the results of clinical trials strengthen the current evidence that hyperthermia combined with chemotherapy is an effective and practical modal-

ity that should be integrated in the present cancer treatment armamentarium.[150]

Recognizing that MNPs can act simultaneously as both mediators for MNH and drug carriers, it is highly feasible to design and fabricate drug-incorporating magnetic nanocomposite devices for multimodal cancer treatment of thermochemotherapy, to realize the possible thermal enhancement to drug cytotoxicity. We have conducted a series of research work in magnetic nano-thermochemotherapy. Due to the space limit, we will give only a brief introduction to the research ideas on magnetic thermochemotherapy mediated by drug-loaded magnetic nanocomposite devices. Detailed information in this topic can be found in our previous publications.[22,114,115,151,152]

5.2.2. Magnetic nano-drugs

In relation to the multimodality treatment by thermochemotherapy, the intention for the design of nanocomposite devices is to use MNPs as one single tool for the combination of hyperthermia and chemotherapy to reach an enhanced therapeutic effect. So far, a series of protocols has been developed for engineering the two moieties within a single nanoplatform. "Magnetic nano-drug by surface modification" is an approach to conjugate or attach drug molecules to the surface of MNPs. A number of physical or chemical approaches have been developed for the conjugation or attachment of functional molecules on MNP surfaces, which can be categorized into covalent linkages and physical interactions, as illustrated in Fig. 3.

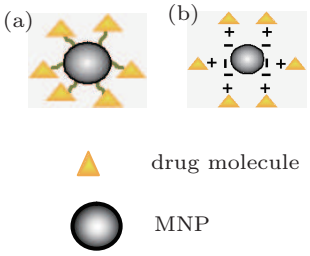


Fig. 3. Schematic diagram of nano-drugs. a: magnetic nano-drug by covalent linkage; b: magnetic nano-drug by electrostatic interaction.

The physical interactions mainly include electrostatic, hydrophilic/hydrophobic, and affinity interactions. For some charged drug molecules, electrostatic interactions are particularly useful in the assembly of magnetic nano-drugs, for instance, cisplatin-functionalized MNPs.[153] Cisplatin is a platinum-based chemotherapy drug used to treat various types of cancers. To fabricate a cisplatin magnetic nano-drug, the SPION cores were coated by a soluble starch derivative so that particles were negatively charged with zeta potential of -41 mV, allowing electrostatic binding of positively charged aquated cisplatin molecules.

In contrast with the physical interactions, a much broader spectrum of approaches has been developed based on the covalent linkage or chemical coupling strategy. Veiseh *et al.* summarized that covalent linkages mainly comprise three approaches: direct nanoparticle conjugation, click chemistry, and covalent linker chemistry.[79] The unique advantages and drawbacks of each of the three approaches have been addressed in detail. Here, we report the fabrication and characterization of an epirubicin-immobilized magnetic nano-drug that may potentially be applied for thermochemotherapy.

Epirubicin is an anthracycline drug used for chemotherapy, which acts by intercalating DNA strands. In order to immobilize the epirubicin molecules onto the surface of MNPs, a conjugation strategy by linker chemistry was adopted. Briefly, polyarylic acid (PAA) was applied as the coating material to introduce carboxyl groups onto the SPION surfaces. The amino group of epirubicin can be conjugated with SPIONs via amide bonds by applying the carbodiimides (EDC) and N-hydroxysuccinimide (NHS or sulfo-NHS) as the chemical linkers. Further characterizations showed that the as-synthesized magnetic nano-drug possessing excellent inductive heat property upon exposed under AMF and magnetic heating can facilitate the drug release from the MNPs. Assessment of the viability of gastric cancer SGC-7901 cells after various treatments showed that mono-treatment treatment by hyperthermia or epirubicin released from magnetic nano-carriers could retard proliferation of the cells. When the bi-modal treatment was applied on the cells, a significantly greater decrease in cell viability can be observed ($p < 0.05$), indicating an intensity effect of nanothermotherapy on epirubicin treatment.

5.2.3. Solar-planet structured magnetic banocomposite devices

Although surface modification chemistry provides a versatile tool for conjugating drug molecules onto the MNPs surface, there are still some restrictions for this strategy. It was suggested by Veiseh *et al.* that the chemistry to be employed should be chosen on the basis of the chemical properties and functional groups found on the SPION coating and ligand to be linked.[79] For most drug molecules, there are no proper functional groups nor is it convenient to introduce such a functional group onto the MNP surfaces for further conjugation. Besides, SPIONs applied in MNH are normally hydrophilic, whilst numerous drugs are not soluble in water, therefore it is very challenging to find an appropriate medium to carry out the modification chemistry. We thus designed the so-called solar-planet structured devices for the combined thermochemotherapy. In the present study, docetaxel is used as a model small molecule anticancer drug, which is a poorly water-soluble, semi-synthetic tax-

ane analog commonly used in the treatment of breast cancer, ovarian cancer, small and non-small cell lung cancer, prostate cancer. For the purpose of fabricating the solar-planet structured devices, docetaxel-loaded polymeric nanoparticles (DNPs) composed of carboxylic-terminated poly(D,L-lactic-co-glycolic acid) (PLGA) with vitamin E TPGS as emulsifier for sustained drug release were prepared by a modified solvent extraction/evaporation technique. Intensive investigations have been carried out for the DNPs and the detailed fabrication protocols of DNPs can be found in our published work.[154] The size of the DNPs fabricated by solvent evaporation methods is around 200 nm. Furthermore, the MNPs modified with amino groups could be covalently attached to the surface of carboxylic terminated DNPs to form the so-called solar (DNPs)-planet (MNPs) structured MNC by EDC/NHS crosslinking protocol as described previously. The fabrication protocol for the solar-planet structured magnetic devices is illustrated in Fig. 4.

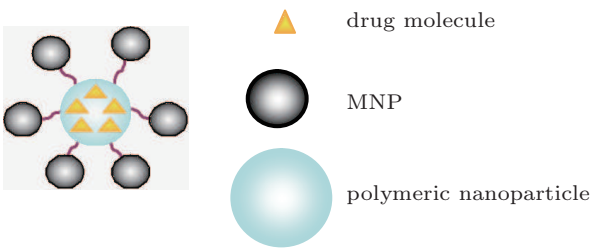


Fig. 4. Illustration of solar-planet structured magnetic nanocomposite device.

5.2.4. Drug-loaded magnetic nanocomposite implant

Unlike the above-mentioned two formulations, which were in colloid or suspension form and were administered by direct intra-tumoral injection, the drug-loaded magnetic nanocomposite implant was designed for post-surgical cancer treatment, mainly for preventing local recurrence of malignant gliomas. Currently, surgical debulking of an accessible tumor in a patient's brain is the conventional clinical treatment for glioma. However, the amount of tumor removed is often limited by proximity to critical regions for brain function, thus resulting in risk of tumor re-growth from residual tumor. It is widely acknowledged that the use of surgically implanted local release systems made of biodegradable polymers for drug delivery over extended periods of time has good potential in glioma treatment. Gliadel®(polifeprosan 20 with carmustine implant) has been approved by the US FDA for use in post-surgical local chemotherapy against recurrent malignant glioma.[155] By co-incorporating the drug and MNPs within the polymeric matrix, the drug-loaded nanocomposite implant can realize both local drug delivery and magnetic hyperthermia simultaneously. Figure 5 is a schematic diagram of the composite implant. Such an implant can be easily prepared by a solvent evaporation method, and a typical implant is flexible, smooth, and homogeneous (as shown in Fig. 6). An *in vivo* study was performed on tumor-bearing nude mice. Xenografts of human glioma cell lines were established by subcutaneous inoculation of U251 MG cells into the hind legs of BALB/c nude mice. For animals in both placebo and experimental groups, a small incision by aseptic surgery was performed on the skin and the tumor was reached after which 3/4 of the tumor volume would be carefully excised. The implants would then be placed well onto the residual tumor bed and subsequently the wound would be closed using subcutaneous suturing. Mice were then exposed under the AMF for 30-min treatment and the temperature of the tumor site was about 46 °C. The body temperature was not affected, the mice did not have symptoms of dehydration and all of them survived the whole experiment of two weeks. Tumors in the thermochemotherapy group shrunk most significantly, as compared with those of the control groups and hyperthermia treatment only.

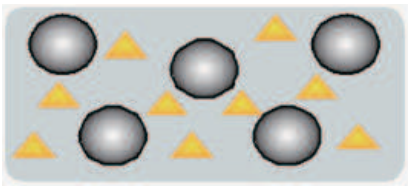


Fig. 5. Illustration of drug-loaded magnetic nanocomposite implant.

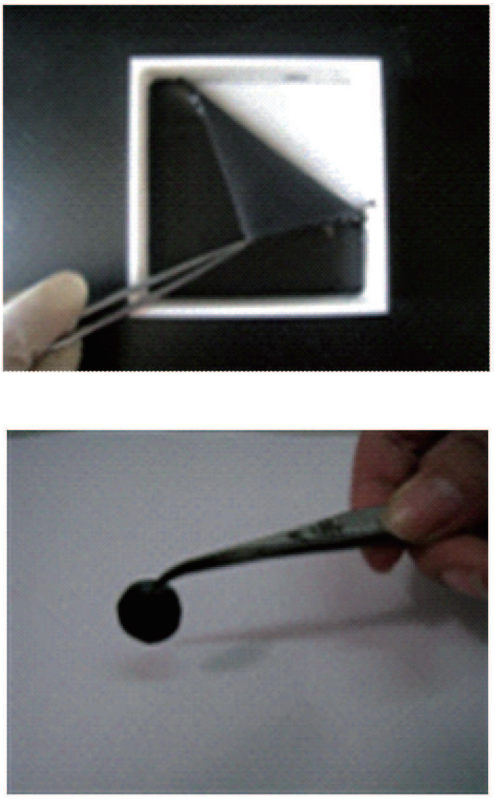


Fig. 6. Docetaxel loaded magnetic nanocomposite implant prepared by solvent evaporation method.

Except for the above-mentioned MNC devices, drug encapsulated magnetic cationic liposome (MCL) thermoresponsive core–shell MNPs, drug-loaded magnetic polymeric nanoparticles, and drug-loaded magnetic polymersomes have been extensively investigated for the bi-modal therapy of combined hyperthermia with chemotherapy[156–160] (Shinkai 2004; Purushotham 2010). The nanocomposite devices exhibit advantageous features for facilitated drug delivery from the nano-carriers, and the magnetic-mediated heating potential is adequate for hyperthermic treatments. We thus conclude that even though further detailed investigations are still necessary, tentative use in local tumor therapies aiming at a specific chemotherapeutic release in combination with magnetic heating is promising and feasible in the long term.

6. Conclusions and remarks

Rapid progress has been witnessed in the research and development of MMH, and the success in clinical trials suggests MMH treatment is a well-tolerated and safe cancer therapy. It is very significant to note that fewer than 50 years passed between the 1957 proposal of the MMH concept and the 1996 completion of phase I clinical trials. The remarkable progress also leaves great space and opportunity for further improvement and optimization of this therapeutic approach. The overwhelming issue is about the SAR value of the MNPs. It was argued by Hergt, who has expanded on the work of Rabin, that in order to heat a 3-mm cluster of cells, the SAR of the MNPs must be unrealistically high, certainly several orders of magnitude greater than is currently reported.[161,162] Consequently, the limited SAR values must require extremely high concentrations of MNPs for a sufficient thermal enhancement. Indeed, a rather high concentration of 100 mg/mL∼120 mg/mL MNPs was applied during the clinical treatment of brain tumor. The high concentration and the difficulty of forming a homogenous MNP distribution with respect to the tumor site by direct injection leads to destruction of normal tissues surrounding the tumor. To solve the problem, much attention has been given to the synthesis of MNPs with super-high SAR values. However, as mentioned earlier in the paper, SAR value is not the only criterion for evaluating the suitability of MMH agents. Other issues, especially biocompatibility and non-toxicity, must be fully considered. Aside from improving the SAR values of MNPs, the inductive heat can also be enhanced by increasing the strength and frequency of the AMF, but only with limited scope. The machine developed by the Jordan group for clinical application operates at 100 kHz and field intensity up to 18 $kA{\cdot}m^{-1}$.[135] It was also observed that patients under MMH treatment for prostate cancer were able to tolerate up to 5 $kA{\cdot}m^{-1}$ for an hour or so but any increase in field intensity would result in some discomfort. Moreover, it was reported by Ito *et al.* that higher frequencies such as those over 400 kHz would cause non-specific heating due to eddy current.[163]

In parallel with the rapid progress in fabrication of high performance magnetic agents and clinical trials, further basic studies regarding MMH should also be carried out, such as heat dissipation theory in MNH, effects of AMF exposure during hyperthermia, endocytosis of MNPs by carcinoma cells, as well as the uniqueness of the cellular or molecular basis of MMH. In a very recent research work, it was reported that cell membrane permeability induced by MNH is significantly greater than that induced by hot water hyperthermia under same temperature conditions.[164] It is therefore an exciting challenge for future endeavors to explore MMH, for its potential in cancer treatment as well as in-depth basic understanding.

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