HHS Public Access

Author manuscript

*J Control Release*. Author manuscript; available in PMC 2016 December 10.

Published in final edited form as:

*J Control Release*. 2015 December 10; 219: 76–94. doi:10.1016/j.jconrel.2015.09.039.

# Magnetic Nanoparticles and Nanocomposites for Remote Controlled Therapies

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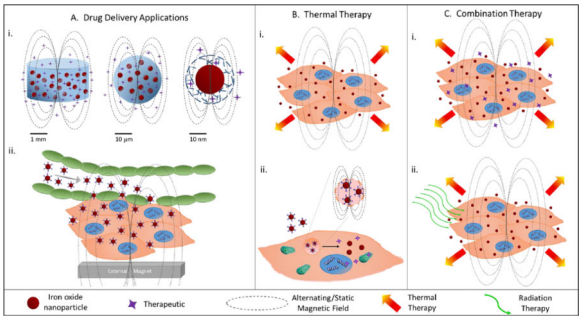
## Abstract

This review highlights the state-of-the-art in the application of magnetic nanoparticles (MNPs) and their composites for remote controlled therapies. Novel macro- to nano-scale systems that utilize remote controlled drug release due to actuation of MNPs by static or alternating magnetic fields and magnetic field guidance of MNPs for drug delivery applications are summarized. Recent advances in controlled energy release for thermal therapy and nanoscale energy therapy are addressed as well. Additionally, studies that utilize MNP-based thermal therapy in combination with other treatments such as chemotherapy or radiation to enhance the efficacy of the conventional treatment are discussed.

## Graphical abstract




This review highlights the uses of MNPs for controlled release therapies. A) Drug delivery applications are divided into i) controlled drug release from a system containing MNPs upon exposure to an alternating or static magnetic field and ii) magnetic guidance. B) Thermal therapy can be remotely controlled for i) local applications or ii) nanoscale heating applications. C) Thermal therapy is often administered in combination with a secondary treatment such as i) a therapeutic or ii) radiation.

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## 1. Introduction

Magnetic nanoparticles (MNPs) have been extensively studied for a variety of biological applications such as FDA-approved MRI contrast agents [1], FDA-approved iron deficiency treatment [2], thermal therapy, and drug delivery. MNPs are often coated with or embedded in a polymer or organic matrix in order to: increase colloid stability and extend circulation time in biological environments, provide a means for functionalization with targeting agents or fluorescent markers, or afford the opportunity for drug loading and conjugation [3–10]. MNPs are able to convert energy from an alternating magnetic field (AMF) to heat, primarily through Neel and Brownian relaxations, with Neel relaxation being the internal dipole rotation and Brownian referring to the physical rotation of the nanoparticle. The heat generated by the MNPs in the presence of an AMF can be utilized for a variety of therapies, including controlled release of a drug, local thermal therapy, nanoscale energy delivery, and combinational treatments. Additionally, MNPs respond to static magnetic field gradients and low frequency AMFs where the heating effect is negligible or non-existent, allowing for other controlled drug delivery strategies, including external guiding/targeting of magnetic nanoparticles and mechanical deformations/disruptions for triggered release.

The unique capability of MNPs and their composites to be remotely controlled has been utilized for various applications [11–20]. When applied in drug delivery, the remote control of the MNPs enables for controlled drug delivery (temporal and/or spatial). For temporal control, the remote actuation is often based on the AMF remote heating of MNPs to cause a temperature-responsive change in the delivery system release properties. In other cases of temporal control, the remote actuation is based on static or low frequency magnetic fields where the mechanical forces induced by the magnetic field result in modulation of the release behavior. For spatial control, the applied magnetic field can remotely control the accumulation of a delivery system within the body. In many cases, enhanced therapeutic delivery and associated outcomes have been reported as a result of the remote control over the temporal and/or spatial release of a drug.

Magnetically mediated hyperthermia (MMH) treatment, also referred to as magnetic fluid hyperthermia (MFH) is another important application of MNPs. MMH is the heating of tissue to hyperthermia temperatures of approximately 41–45°C by activation of the MNPs in the presence of an AMF. This inherently localized heating therapy has been studied extensively for cancer therapy both in isolation or combination with a conventional cancer therapy such as chemotherapy or radiation [15, 21–26]. Localized thermal therapy via MMH has been shown to be more effective than other forms of hyperthermia delivery.

MMH has also been shown to enhance the efficacy of traditional cancer therapies such as chemotherapy, radiation, surgical resection, and gene therapy. A variety of chemotherapeutics are more effective when administered in the hyperthermia range due to increased rate constants of alkylation, increased drug uptake, and inhibition of repair of drug-induced lethal or sub-lethal damage [27]. Chemotherapeutics have also been chemically or physically bound to magnetic nanoparticles for controlled drug release upon exposure to an external stimuli such as an AMF or change in pH, and upon further exposure

to AMF, simultaneous thermal therapy can be administered [19, 28, 29]. Additionally, hyperthermia has been shown to increase blood supply to the tumor, which increases local oxygen levels. Since the efficacy of radiation therapy is tied to the formation of free radicals more than direct DNA damage, MMH can enhance the effectiveness of radiation by increasing free radical formation. Overall, thermal therapy via MNPs is a promising treatment method when combined with traditional therapies due to localized tumor heating and sensitization of the tumor tissue to additional modalities.

One of the major translational hurdles of MMH is that a large concentration of nanoparticles is required to achieve the necessary increase in temperature *in vitro* and especially *in vivo*, and this limitation, to date, has limited the application of MMH to direct injection into solid tumors for *in vivo* application [30, 31]. Therefore, researchers have recently focused more on magnetically mediated energy delivery, termed MagMED, for nanoscale energy therapy [32]. This form of therapy utilizing AMF-activated MNPs relies on intracellular effects of MNPs and results in a therapeutic effect without a measurable temperature rise, with the exact mechanism of toxicity still under investigation. Intracellular concentrations of MNPs can be increased by cellular targeting with ligands and antibodies, which has been shown to further enhance the effectiveness of MagMED as a treatment modality [4, 6, 7, 33, 34]. Therapeutic approaches based on MagMED have led many researchers to focus on determining intracellular targets and understanding intracellular mechanisms.

This review summarizes recent advances in applications of MNPs and magnetic nanocomposites for remote controlled therapies (Schematic 1). Remote controlled drug release from MNPs and their composites that range from macro- to nano-scale are addressed, as well as other remotely guided systems for drug delivery. In addition, more recent advances in nanoscale energy delivery, thermal therapy, and combination therapies are presented.

## 2. Remote controlled drug therapy

### 2.1 Magnetic field triggered release

In the first demonstrations of remote controlled release using magnetic fields, macroscale or microscale permanent magnetics were embedded into polymer films or microparticles, and these composite materials were demonstrated to exhibit pulsatile release when exposed to periodic magnetic fields [35–45]. In these early examples, the oscillating magnetic fields were at a low frequency (few to tens of Hz) and amplitudes of a few hundred to couple thousand Gauss, and the authors demonstrated great potential of remote controlled delivery systems with multiple example therapeutics. In this section, we focus on the remote controlled release of systems containing MNPs. MNPs have been widely studied for remote controlled drug delivery applications where their response to an applied magnetic field (static or alternating) results in a modulation of the release rate of an entrapped or attached drug. In many applications, an AMF at frequencies typically greater than 10 kHz has been used to remotely heat MNPs, and then, the local heating within the delivery system alters the drug releasing properties. Here, sections are included that highlight the developments in macro- and micro-/nano-scale systems that incorporate MNPs for remote controlled drug delivery applications.

**2.1.1 Macroscale composites for triggered release—**In this section, we highlight recent efforts that use magnetic fields to either remotely heat a material/system or remotely manipulate a material/system through magnetic forces. The first few examples focus on remote controlled release of drugs through the heating of a material/system in the presence of an AMF, and then, a few examples of modulated release, where a static magnetic field or low frequency magnetic fields were used and there is no heating of the MNPs, are presented.

Researchers have applied the remote heating capability of MNPs to trigger various thermal transitions in macroscale materials or systems [46–63], and in the following, we highlight a few recent examples of novel materials and systems where AMF triggered thermal transitions resulted in modulated release of a drug. In one strategy, Campbell et al. developed nanocomposite systems designed to be in situ-gelling and thus injectable [48, 49]. For example, they recently developed nanocomposite in situ-gelling hydrogels that were composed of MNPs and thermoresponsive microgels, and these systems were demonstrated to have approximately a 4-fold enhancement in release of a model drug (4 kDa fluorescein labeled dextran) when exposed to an AMF (200 kHz) [48]. It was also shown that these systems were able to maintain pulsatile release properties over multiple cycles and multiple days.

In another example of a thermoresponsive injectable systems, Hawkins et al. developed a nanocomposite sol-gel system based on Pluronic® F-127 and iron oxide MNPs [46]. When exposed to an AMF (296 kHz, 27.9 kA/m), it was demonstrated that pulsatile release of lysozyme could be achieved, although only over short time frames for the system composition studied. Another study by Hoare et al. developed magnetically triggered nanocomposite membranes based on poly(N-isopropyl acrylamide) nanogels and iron oxide MNPs dispersed in ethyl cellulose as the membrane material [50, 51]. In their most recent study [51], an AMF (220–260 kHz, 0–20 mT) was used to heat the membrane and trigger the release of sodium fluorescein as a model drug.

Rovers et al. developed novel polymer implants (Figure 1a) that consisted of a poly(methyl methacrylate) core encompassing dispersed iron oxide MNPs and a thermoresponsive coating based on poly(butyl methacrylate-stat-methyl methacrylate) containing ibuprofen as a model drug [54]. In this design, the thermoresponsive switch was based on the significant change in the diffusivity of the drug in the polymer coating when the temperature of the polymer coating increased above its glass transition temperature. Using an AMF (745 kHz, 2.85 kA/m), it was demonstrated that an on/off ratio of approximately 17 was achieved under physiologically relevant conditions (Figure 1b).

A novel monoglyceride-based thermoresponsive drug delivery system was developed by Mengesha et al. [55]. Specifically, nanocomposite lipid matrices containing mixtures of glyceryl monooleate (GMO) and glyceryl monostearate (GMS) with oleic-acid coated iron oxide MNPs were prepared (Figure 1c). These matrices were loaded with nifedipine as a poorly water-soluble model drug. AMF (300 kHz, 57.0 kA/m) exposure caused the matrices to undergo a phase transition, and a corresponding burst of nifedipine release was observed as shown in Figure 1d. When the AMF was removed, the release rate reduced because the monoglyceride matrix recrystallized as the system returned to 37°C. The above examples

illustrate the wide variety of designs and strategies that have been successfully used to modulate the release of a drug from a material/system due to local heating when exposed to an AMF.

In addition to the various strategies to remotely control the release of drugs using the heating properties of MNPs under exposure to an AMF, various groups have explored ways to achieve modulated release using a static magnetic field or low frequency magnetic fields, where there is no heating of the MNPs [64–74]. In the following, some of the more recent examples are highlighted. Cezar et al. recently developed a biphasic alginate-iron oxide ferrogel that was capable of large deformations and triggered release (Figure 2a) [68]. When exposed to a magnetic field for 2 minutes at 1 Hz every 2 hours, the pulsatile release of mitoxantrone as a model drug was demonstrated (Figure 2b). Additionally, the pulsatile release of viable cells was shown, when exposed to a magnetic field for 2 minutes at 1 Hz every 24 hours (Figure 2c). Another example by Cai et al. demonstrated pulsatile release of DNA and vitamin B12 as model drugs from a biodegradable polymeric multireservoir device [71]. The device was fabricated with a poly(D,L-lactic acid) biodegradable substrate and porous polycarbonate (average diameter of 125 ± 13.2 nm) as a sealing membrane. Iron oxide MNPs were loaded in the reservoir, and when exposed to a static magnetic field of sufficient magnitude, the MNPs aggregated and sealed the pores. In other work, Guilherme et al. demonstrated an increase in albumin release rate under exposure to a continuous magnetic field from a superabsorbent hydrogel composite based on vinyl-modified starch, acrylic acid, and N,N-dimethylacrylamide containing iron oxide MNPs [69].

**2.1.2 Micro- and nanoscale composites for triggered release—**Micro- and nanoscale systems have the advantage of easier administration through injection routes (e.g., subcutaneous, intramuscular, intravenous, etc.), and for this reason, smaller scale systems have received significant attention in recent years. Microscale systems have been developed to provide modulated release in the presence of applied magnetic fields of various frequency, where heating, mechanical effects, etc. cause a change in material properties and result in controlled drug delivery [75–84]. In addition, numerous researchers have worked to develop magnetic nanocomposite systems with submicron dimensions, which allows for systemic delivery and treatment. Researchers have applied the remote activation of MNPs to trigger various thermal transitions, mechanical effects, or combinations of these in nanoscale materials. In this section, some of the recent submicron examples will be highlighted.

Magnetoliposomes have been widely studied for various biomedical applications [85–87]. For controlled drug release, researchers have used localized heating and/or mechanical actuation of MNPs to manipulate the liposomal permeability to a loaded drug [88–102]. For example, Katagiri et al. developed hybrid liposomes composed of phospholipids, iron oxide MNPs, and thermosensitive block copolymers [89]. These hybrid liposomes were shown to have enhanced release of a model drug pyranine) when exposed to an AMF (360 kHz, 234 Oe) and negligible release without exposure to an AMF. The enhanced release was primarily attributed to the transition in the thermosensitive block copolymers due to heating of the MNPs. Recently, Guo et al. developed carboxymethyl dextran-coated magnetoliposomes and demonstrated the modulated release of doxorubicin with exposure to a low frequency AMF (50 Hz, 15–45 mT) [101]. The release rate of doxorubicin increased with increasing

amplitude of the applied AMF, with 45 mT being the highest amplitude and greatest rate of release. As expected, at this frequency and amplitude range, there was no observed temperature rise in the system. This ability to modify release with a low frequency AMF and without a temperature rise is potentially advantageous for clinical applications. In the last few years, Peiris et al. have developed a new platform for remote controlled release based on nanochain particulates that contain a liposome attached to three functionalized MNPs [103–106]. In the first demonstration of this platform for remote controlled delivery, it was shown that the nanochains responded to an AMF (10 kHz, 2 mT) resulting in an increased release of a doxorubicin [104]. The authors concluded that the increased rate of release was a result of primarily mechanical effects and induced defects in the liposomal walls during the exposure to the AMF. More recently, these nanochains have been applied in cancer therapy applications, including the treatment of breast tumors and brain tumors.

In addition to liposomes, various other nanoparticle platforms have been used for remote controlled drug delivery using an AMF. In several cases, MNPs have been combined with silica to create composite nanoparticles that can be remotely stimulated to trigger release [107–114]. Numerous other cases incorporate MNPs into polymer-based nanoparticles (e.g., polymer micelles, polymersomes, etc.) where the energy delivered by an AMF modulates the delivery of a therapeutic from the nanoparticle system [115–135]. For example, Hu et al. used a double emulsion approach to prepare composite nanocapsules based on a block copolymer of polystyrene and poly(allyl alcohol) that was able to incorporate both hydrophilic and hydrophobic compounds as well as oleic acid-coated MNPs (see Figure 3a) [115]. The release rate of a model hydrophilic compound (FITC-labeled plasmid DNA) and a model hydrophobic compound (pyrene) were both modulated with exposure to an AMF (50 kHz, 0–2.0 kA/m). The field amplitude was varied from 0 kA/m to 2.0 kA/m, and the magnitude of the pulsed release was shown to increase with the increasing field amplitude (see Figure 3b). Another study by Qu et al. encapsulated both hydrophobic MNPs and camptothecin into polymer nanoassemblies of a thermosensitive amphiphilic polymer (polylactide-b-poly(N-isopropyl acrylamide-co-N,N-dimethacrylamide) [119]. The release rate of camptothecin was shown to significantly increase when exposed to an AMF (114 kHz, 89.9 kA/m).

As an alternative to the various composite nanoparticle examples above, researchers have also explored methods for directly conjugating a drug molecule to the surface of MNP-based core particles [136–141]. In early work by Derfus et al., a 30 base pair (bp) DNA strand was conjugated to a dextran-coated iron oxide MNPs, and a complement of 12, 18, or 24 bp that was linked to a fluorophore as a model drug was bound to this surface tethered DNA [136]. An AMF (400 kHz and varying power) was demonstrated to melt primarily the 12 bp complement and higher powers led to simultaneous melting of the 12 and 24 bp complements. Recently, Nair et al. demonstrated the remote controlled release of an anti-HIV drug that was tethered to a magneto-electric nanoparticle with a MNP core composed of cobalt ferrite and a $BaTiO_3$ shell [137]. The frequency (0, 100, and 1000 Hz) and amplitude (12, 44, and 66 Oe) of the AMF was varied, and the release of an anti-HIV drug was demonstrated to be dependent on both the frequency and amplitude of field (Figure 4a). At these low field frequencies and amplitudes, there is not expected to be any heating

effects. The authors concluded that the magneto-electric properties of the nanoparticles lead to the coupling of magnetic field with electric forces in the drug-carrier bonds (Figure 4b).

### 2.2 Magnetic field targeted delivery

Magnetic nanoparticles are particularly interesting due to their multimodal targeting potential. MNPs can passively target by the enhanced permeation and retention effect (EPR) in cancer applications and actively target by either magnetic fields (i.e. magnetic guidance) or surface modification with targeting ligands. Each of these modes of targeting has previously been reviewed, and the reader is pointed to some of these publications for a more conclusive look into passive targeting via EPR [142–144], active targeting through surface modification [145–147], and magnetic guidance [14, 18, 21, 148–153]. In this section, some of the early work and recent highlights in magnetic guidance are presented.

Guiding magnetic material to specific regions within the body has interested researchers for over 30 years [21, 154–157]. Nearly 20 years ago, Lubbe et al. were the first to attempt magnetic guidance in a clinical setting [158]. The rationale behind magnetic guidance is consistent with all other targeted drug delivery systems wherein localizing the therapy increases the potency within the desired tissue while reducing side effects in other areas of the body.

Recently, Schleich et al. compared the three different modes of targeting, as well as dual targeting, *in vivo* by administering PLGA nanoparticles loaded with MNPs and paclitaxel, with and without surface modification [159]. In this work, CT26 colon carcinoma cells were injected in the right flank of BALB/c mice before treatment and the mice were split into the following 4 treatment groups: 1) PBS control, 2) passive targeting, 3) active targeting with surface modification, 4) active targeting by magnetic guidance, and 5) dual active targeting by surface modification and magnetic guidance. For groups 4 and 5, the surface of the PLGA particles was modified with RGD peptide in order to actively target $\alpha_v\beta_3$ integrin, which is commonly over expressed in tumor cells. The results of these studies showed a 2.5-, 5-, and 8-fold increase in tumor accumulation for groups 3 (RGD targeting), 4 (magnetic guidance) and 5 (dual RGD and magnetic guidance), respectively compared to passive targeting. Additionally, mice in group 5 survived longer and had slower tumor progression, thereby illustrating the potential of dual active targeting with surface modification and magnetic guidance.

One particularly interesting application of magnetic guidance is in vascular stents [160]. Here, post-surgical re-obstruction of the vasculature, called in-stent restenosis, can require local delivery of therapeutic agents [14, 148]. Chorny et al. reported successful magnetic targeting of stented regions within Sprague-Dawley rats [161]. In this work, stainless steel stents were magnetized by a uniform magnetic field (1,200 G) at a distance of 40 mm from each side of the mouse and paclitaxel-loaded MNPs were injected. After injection, the field was maintained for 5 minutes, and the results showed a 4-fold higher MNP concentration compared with control animals.

Additionally, a recent study from this same group examined the potential of magnetic targeting for site-specific gene delivery in a rat carotid model of stent angioplasty [162]. The

authors loaded zinc oleate MNPs with an adenoviral (Ad) vector (MNP(Ad)s), examined gene transfection *in vitro*, and delivered the particles to male Sprague-Dawley rats with stainless steel stents on the left external carotid artery. For the animal studies, a magnetic field of 1.2 kOe was generated by positioning a pair of electromagnets 40 mm from each side of the mouse and was maintained for 5 minutes after MNP(Ad)s were injected. Their results showed a significantly stronger reporter expression (firefly luciferase) for the magnetically targeted MNP(Ad)s. Quantification of the bioluminescence showed a 14- and 8-fold increase in bioluminescence for the magnetically targeted MNP(Ad)s relative to the non-targeted MNP(Ad)s and free Ad, respectively. However, quantification of reporter enzymatic activity in homogenized tissue showed 38-fold higher gene expression for the magnetically targeted MNP(Ad)s relative to the non-targeted MNP(Ad) controls thereby suggesting higher sensitivity for this assay.

Another relatively new application of magnetic guidance is the use of magnetic fields to direct aerosols containing magnetic particles to preferentially accumulate in desired regions of the lungs. This method is particularly attractive for patients with diseased lungs, as it combines two degrees of targeting; physical targeting of the affected tissue is accomplished through pulmonary delivery while magnetic guidance to specific regions within the lungs enhances the desired outcome. To the author's knowledge, the first report of magnetically guided aerosols for therapeutic applications was in 2005 by Ally et al. This work described theoretical concepts of magnetic aerosols and laid the experimental foundation for enhancing deposition of aerosols containing magnetic particles [163].

The Rudolph group published a recent study where they delivered magnetic aerosols containing model drugs to BALB/c mice via voluntary inhalation of nebulized liquid droplets [164]. In this work, the authors used mathematical simulations to optimize a portable magnet consisting of four identical magnets arranged in a quadrupole and attached this magnet the chest of the mice during inhalation. This quadrupole resulted in a magnetic field of 0.2 Tesla and a magnetic gradient of 140 $Tm^{-1}$, 2 mm from the surface of the magnet, which is the distance they estimated between the animals' chest and the lung tissue and ensured a strong magnetic field in the vertical direction. The MNP content in the lungs of these mice was determined using a previously reported method of magnet relaxometry [165] and colorimetric determination of non-heme. Both methods revealed a 2.1-fold increase in the targeted right lung (relative to the untargeted left lung) of the animals (no difference was measured in absence of magnetic field). Additionally, a plasmid DNA (coding for the reporter gene *luciferase*) was functionalized with 25 kDa PEI and added to the magnetic aerosol suspension. The *in vivo* bioluminescence was measured 24 hours after inhalation (using an IVIS-100 system) and the transgene expression is illustrated in Figure 5.

*Ex vivo* quantification of luciferase (Figure 5c) confirmed the findings of the bioluminescence. Additionally, histopathological analysis revealed no alterations in the lungs of mice after inhalation of magnetosols. These studies show the potential of MNPs in pulmonary delivery by confirming the ability to provide two levels of active targeting through inhaling MNPs directly to the lungs and magnetically guiding them for site-specific accumulation.

## 3. Remote controlled energy release

### 3.1 Thermal therapy

Magnetic nanoparticles have been extensively studied for thermal therapy applications due to their ability to convert energy from an AMF into thermal energy. This controlled release of thermal energy from MNPs can be used for hyperthermia treatment, which is defined as the heating of tissue to 41–45°C [166] and has been shown to be an effective treatment of various types of cancer. Conversely, some have suggested that the efficacy of hyperthermia is likely due to tumor tissue being more susceptible to heat insults than healthy tissue [167, 168]. Magnetically mediated hyperthermia (MMH), which is also known as magnetic fluid hyperthermia (MFH), is where MNPs or larger magnetic particles are localized within the tumor environment and then exposed to an AMF, resulting in heat generation. For cancer therapy, MMH has several advantages over other delivery routes of thermal therapy in that it is localized to only the tumor tissue through selectively targeting (e.g., active or passive targeting, direct injection, etc.) and provides even temperature distribution throughout the tumor tissue. By comparison, regional and whole body hyperthermia are used to heat larger regions such as a limb or cavity, or to treat metastatic disease, but often lead to undesirable damage of healthy tissue. Beyond delivering thermal energy, MNPs have additional physical properties that make them advantageous for thermal delivery such as physical rotation of the nanoparticle in the presence of an AMF [169], elevated nanoparticle surface temperatures [170], and result in increased intracellular temperatures following nanoparticle uptake [33, 171]. These are all potential explanations to the improvement of MMH over other hyperthermia treatments.

This improvement was demonstrated by Rodriguez-Luccioni et al. when they addressed the effects of MMH using MNPs functionalized with carboxymethyl dextran compared to hot water hyperthermia (HWH) on MCF-7 and Caco-2 cells [172]. MMH resulted in a greater decrease in cell viability for both cell lines compared to HWH. A thorough review of MMH using iron oxide nanoparticles and the mechanisms of heat dissipation was written by Laurent et al. in 2011 [173], and others have addressed the advances, challenges, promises, and perils of MNPs for hyperthermia applications [32, 174]. Therefore, this section focuses on recent studies that utilize controlled delivery of thermal energy from MNPs and the therapeutic and immunotherapeutic effects of the treatment.

Several research groups have studied the efficacy of magnetically mediated thermal therapy as a treatment modality for cancer both *in vitro* and *in vivo* [31, 175–187]. Thermoablation is another form of thermal therapy induced by raising the bulk solution temperature above 45°C. A recent review highlights the use of various nanomaterials, including MNPs, for thermoablative treatment, imaging, and diagnostics [188]. The temperature at which the thermal therapy is performed dictates cellular response, with apoptosis being linked to hyperthermia temperatures and necrosis being associated with thermoablation. Both of these thermal therapy treatments can be administered via MNPs in the presence of an AMF, but it is important to understand the properties of magnetic nanoparticles in cellular environments in order to synthesize magnetic nanoparticle systems with the potential for maximum energy delivery. Di Corato et al. analyzed energy delivery by magnetic nanoparticles in a cellular

environment and compared it to nanoparticles in suspension [189]. In all systems, there was a systematic decrease in the heating efficiency for nanomaterials associated with tumor cells, which was likely due to inhibition of the Brownian relaxation in cellular conditions. The magnitude of this decrease was associated with the type of nanoparticle, but in general, it was determined that nanoparticles in the superparamagnetic domain are minimally effected by the cellular environment.

Various superparamagnetic nanoparticle systems have been developed to improve the efficacy of thermal therapy as a treatment of cancer. Wydra et al. developed an iron oxide nanoparticle system coated with citric acid or poly(ethylene glycol) (400) dimethacrylate (PEG400DMA) via atomic transfer radical polymerization (ATRP) [190]. A549 lung carcinoma were exposed to 10 mg/mL $Fe_3O_4$ and exposed to an AMF (301 kHz, 27.9 kA/m) for 10 minutes resulting in a bulk solution temperature of 55°C in the center of the dish where the magnetic field amplitude was greatest. Minimal cell death occurred in the periphery indicating that temperatures in the thermal ablation range were sufficient at inducing cell death, most likely through necrosis.

Other studies have looked to address the differences between thermal therapies in the hyperthermia and thermoablation temperature ranges [191, 192]. In a study completed by Wang et al., the efficacy of high end hyperthermia treatment (47°C) was compared to thermoablation treatment at 51°C on subcutaneous MPC-83 tumors in female mice [191]. Thermal therapy was administered at temperatures of 47 or 51°C for 30 minutes (300 kHz, 100 G) after the tumors had grown to 10 mm in diameter. After hyperthermia treatment at either temperature, the tumors in the 20 mice disappeared within 14 days. However, subcutaneous nodules of 3 mice in the 47°C group and 2 mice in the 51°C group began to relapse within 2 months after hyperthermia. Additionally, 7/10 mice in the 47°C group and 8/10 in the 51°C group were alive 140 days after hyperthermia treatment. This is a significant increase in survival of the hyperthermia groups compared to the control. In another study by Hu et al., A549 xenograft mice were injected with three different doses of iron oxide MNPs, which resulted in varying tumor temperatures of 41.3, 44.5, and 46.8°C [192]. Tumor temperatures from 42–46°C resulted in disruption of the enzymatic system and structure of the tumor, therefore inducing apoptosis. Above 46°C, numerous large necrotic areas were observed within the tumors, and the nanoparticles were either distributed in the interstitial matrix of tumors or phagocytized by tumor cells.

In addition to cellular death, thermal therapy has a variety of consequences on the tumor microenvironment [193] and tumor growth factor expression [194]. In a study completed by Kolosnjaj-Tabi et al. in 2014, PEG-coated iron oxide nanocubes were injected intratumorally into epidermoid carcinoma xenograft mice and treated for three days with 30 minutes of AMF exposure (111 kHz, 23.8 kA/m), which resulted in a temperature rise of 7.8 ± 2.2°C [193]. This hyperthermia treatment resulted in the slackening of generally compact collagen fibers, which in turn increased nanocube penetration into the cell-rich tumor core. After MMH treatment, the intra-fibrillar space of the collagen matrix was shown to increase from 101 ± 17 nm to 133 ± 32 nm due to a phase transition of the collagen network. Thermal therapy via magnetic nanoparticles has also been shown to down regulate vascular endothelial growth factor (VEGF) in rats with Walker 265 breast carcinoma [194]. Thermal

treatment in the range of 50–55°C was administered 1, 2 or 3 times for 30 minutes via AMF exposure (180 kHz, 55 G) resulting in tumor growth inhibition and promoting the survival of tumor bearing rats. Gene expression of VEGF and its receptors in the tumor were decreased, thereby inhibiting tumor angiogenesis.

Thermal therapy using MNPs in an AMF has also been utilized as an immunotherapeutic treatment with promising results [195–198]. Magnetic cationic liposomes (MCLs) were used for hyperthermia treatment in three of these studies due to their higher affinity for tumors cells than neutrally charged magnetoliposomes. In one of the first immunotherapy treatment studies via thermal therapy, T-9 rat glioma tumors were formed in the left flank of female rats, and MCLs were injected into half the tumors followed by exposure to an AMF (118 kHz, 384 Oe) for 30 minutes (3 times at 24 hour intervals) [195]. 89% of the rats treated with hyperthermia had complete regression. Three months later, cured rats or naïve rats were challenged with T-9 or malignant fibrous histiocytoma cells in the right flank. All right flank tumors (T-9 or malignant fibrous histiocytoma) formed in the mice not initially treated with hyperthermia. Conversely, T-9 right flank tumors did not form in mice treated with hyperthermia in the T-9 left flank tumors. However, malignant fibrous histiocytoma cell injection into the right flank resulted in tumor formation. Therefore, the immune response was found to be specific for the original T9 cells. Additionally, CD3+, CD4+, CD8+, and NK immunocytes were detected in the left and right tumors of mice treated with hyperthermia, but no immunocytes were found in the control group.

A subsequent study was completed on B16 melanoma subcutaneous tumors [196] and showed that 9 out of the 10 mice had complete tumor disappearance 120 days after two 30 minute hyperthermia treatments with MCLs in an AMF (118 kHz). Spleen cells were obtained from the cured mice, and in an *in vitro* study, these cells were shown to have increased cytotoxic activity against B16 cells compared to spleen cells from naïve mice. An *in vivo* immunotherapy study was also completed wherein mice were challenged with B16 melanoma cells 120 days after treatment. In the naïve mice, tumors formed 6 days post inoculation. However, 66% of the cured mice rejected the melanoma cells resulting in no nodule formation. The extended time between hyperthermia treatment and secondary inoculation suggests that MMH has the potential to decrease metastatic potential of B16 melanoma cells.

A more recent study on the immunotherapeutic effects of MMH was completed by Toraya-Brown et al. in 2014 and showed that local hyperthermia treatment induced CD8+ T cell-mediated resistance against distal and secondary tumors [198]. B16 tumors were established in both the left and right flanks simultaneously, but only the left flank tumor was treated with MMH (43°C) for 30 minutes. Right flank tumors of the left flank heated group were found to grow significantly slower than the non-heated group as shown in Figure 6a. Another experiment examined secondary tumor formation in the right and left flanks after a right flank tumor was treated with hyperthermia and then excised three days post treatment. Secondary tumor growth was inhibited on both the primary tumor side and the contralateral side in the heated group compared to the non-heated group (Figure 6b). This study also revealed that the timing of secondary tumor inoculation plays a role in tumor formation. One day after hyperthermia treatment resulted in no resistance to secondary tumor formation

while inoculation 30 days after treatment inhibited tumor growth on the primary side but not the contralateral side. Additionally, it was found that local hyperthermia increases CD8+ T cells – required for inducing resistance against secondary tumors – as the effects of heating the primary tumor were completely abrogated by treating with CD8+ antibiotics to deplete CD8+ formation.

In addition to the *in vitro* and *in vivo* studies completed using magnetically mediated thermal therapy, there have also been a few clinical trials investigating quality of life and feasibility of thermotherapy using magnetic nanoparticles [199, 200]. Maximum temperatures of 55°C were obtained in the prostate using only 25% of the available magnetic field amplitude, and mean intra tumor temperatures were kept between 42 and 46°C for 60 minutes (once per week for 6 weeks). It was determined that this treatment was not enough to kill the cancerous cells but is applicable as a combinational treatment [199]. A quality of life assessment was also completed on this clinical trial, and it was found that quality of life was only temporarily impaired by MNP thermotherapy with urinary symptoms which appeared almost exclusively during the first three weeks of treatment [200].

### 3.2 Nanoscale energy therapy

As discussed above, thermal therapy has been studied for decades, with various successes in MMH and related treatments, but this approach has yet to gain widespread clinical recognition either as an independent treatment or in conjunction with traditional therapies. This section explores the most recent advances in the promising area of magnetically mediated energy delivery (MagMED) therapy, wherein MNPs are engineered for the selective destruction of cells and/or intracellular structures without a macroscopic tissue temperature rise [32].

A major translational hurdle of MMH is that a large concentration of nanoparticles is required to achieve the necessary increase in temperature *in vitro* and especially *in vivo*, thus limiting the application to direct injection into solid tumors for *in vivo* application [30, 31]. Medical imaging would be required to facilitate guided injection into a solid tumor in which the advantages of MMH over traditional surgical resection or other localized treatments would become minimal or nonexistent. While utilizing the enhanced permeability and retention effect has been proposed for systemic delivery of nanoparticles [201, 202], concerns over achieving sufficient tumor accumulation has been raised. When MMH was in its infancy, Gordon et al. hypothesized that intracellular hyperthermia would be more effective than extracellular by overcoming a potential thermal barrier created by the cell membrane [203]. Intracellular hyperthermia would negate the clinical issue of high nanoparticle concentrations as only the cells themselves and not the surrounding tissue would have to be heated to the hyperthermia range. To facilitate nanoparticle internalization, nanoparticles have been functionalized with a wide range of targeting ligands such as peptides, antibodies, small molecules, and carbohydrates [204–209].

Following successful results demonstrating the potential for MMH, researchers turned their attention to intracellular hyperthermia [210–212]. For example, Jordan et al. explored the internalization of dextran and amine functionalized nanoparticles by four cell lines *in vitro* [168]. Based on the internalization, they observed a three-fold decrease in clonogenic

survival by nanoparticle-mediated hyperthermia compared to HWH, thereby demonstrating the potential to deliver heat to the targeted cells. Fortin et al. studied anionic coated maghemite and cobalt ferrite and determined that cancer cells sufficiently internalize the particles at the rate of about 25 pg per cell over the course of 1 hour [213]. These cells were collected and dispersed at a concentration of 20 million cells per 0.3 ml and generated sufficient heating in a magnetic field to achieve the hyperthermia range. The authors explored the heating contributions from the two relaxations and concluded that Neel relaxation is dominant during intracellular hyperthermia as the Brownian contribution was minimized while entrapped in intracellular vesicles. Thus, future design of MNPs should emphasize the Neel contribution. Iron oxide based MNPs can be doped with various transitional metals to generate different physical and magnetic properties to improve the likelihood of successful intracellular hyperthermia [16, 214]. However, concerns over the toxicity of transition metals in the body have stalled future advances.

Despite promising initial results and room for conceptual development, the mechanism and feasibility of intracellular hyperthermia has been debated for over a decade. The debate stems from the heat transport calculations by Rabin that demonstrated, theoretically, that the relative heat transfer should be insufficient to induce damage to a cell [215]. In the paper, Rabin explored three length scales: nanoscale (5–100 nm), microscale (2–20 μm), and macroscale (20 mm). For a typical particle, the steady state temperature difference for a single particle is no greater than $10^{-5}$ °C implying that a single particle is incapable of thermal damage. Scaling up to the microscale, a cluster of nanoparticles close to 200 μm in diameter, which is far larger than a single cell, would be required to achieve a local threshold of 43 °C. If the local scale is changed to just heating a single cell of 15 μm, the heating power required would be two times what is typically achieved in literature. At the macroscale, the analysis modeled a spherical tumor containing uniformly distributed nanoparticles, and it was determined that the minimal diameter required would be 1.1 mm, which limits the therapy to large tumors. All calculations were performed in the absence of blood perfusion, which would add an additional cooling effect to the macroscale calculations.

However, ground breaking work by Creixell et al. demonstrated that internalized targeted nanoparticles can induce cellular death when exposed to an AMF without a measurable temperature rise [33]. The iron oxide MNPs were coated with carboxymethyl-dextran and conjugated with epidermal growth factor (EGF) targeting ligands. The targeted nanoparticles were internalized by breast cancer cells at a greater rate than non-targeted, and when exposed to the AMF (233 kHz, 37.5 kA/m), a 99.9% reduction in cell viability was demonstrated. By utilizing appropriate targeting ligands and this observed intracellular effect where internalized nanoparticles deliver therapeutic gains without perceived temperature rise, the possibility of using magnetic nanoparticles to treat metastatic lesions could be realized instead of being limited to solid tumors. For example, HER2 targeted nanoparticles are not only capable of reaching the primary tumor but micrometastatic sites as well and could be a good targeting ligand for this form of therapy [34]. This potential therapy has been coined as ‘magnetically mediated energy delivery’ (MagMED), and it represents a promising field of therapeutics [32]. The provocative question now facing researchers is the exact mechanism of cytotoxicity, and although studied some, it still needs

further exploration. Possible mechanisms at play are local heating effects, physical-mechanical effects (rotational or vibrational movements), and/or chemical effects, and each of these will be explored below.

Experimental evidence demonstrating local or nanoscale heating usually involves changes in a fluorescent polymeric shell or involves nanoparticles in the direct vicinity of a liposomal carrier increasing the permeability of the bilayer [88, 216, 217]. For example, Polo-Corrales and Rinaldi developed iron oxide MNPs coated with a poly(*N*-isopropylacrylamide) shell and a fluorescently tagged acrylamide incorporated into the polymeric coating [217]. The polymeric shell was temperature responsive with a LCST at 35 °C, and the fluorescence intensity is dependent on the local solvent polarity. It was observed with AMF exposure that the surface temperature of the nanoparticles was able to immediately drive this transition temperature while the solution temperature lagged behind. The localized heating effect observed experimentally may attribute to the cytotoxicity of the therapy by directly heating and damaging local subcellular components.

In the presence of the AMF, the nanoparticles would be physically rotating and realigning themselves in chains along the field. The mechanical forces from magnetic nanoparticle actuation on the range of femto to piconewton have been reported in literature to cluster cellular receptors, distort ion channels, and stimulate the cytoskeleton [218–220]. These mechanical forces could be used to induce apoptosis through lysosomal membrane permeabilization. Increasing the permeability of lysosomes will induce cellular death through the release of cathepsins from the lysosomal compartment into the cytosol where they participate in apoptotic pathways [221–223]. Such a strategy is attractive to researchers as it has been shown to induce cellular death in cancer cells which typically have resistance to apoptotic pathways [224]. In follow-up work with the EGF-targeted iron oxide nanoparticles developed by Creixell et al., Domenech et al. observed that the nanoparticles were specifically being internalized into lysosomal compartments [225, 226]. Upon exposure to the AMF (233 kHz, 42 kA/m), they observed an increase in lysosomal permeability and decreased viability as a result of their intracellular treatment. They attributed this observation to either heat dissipation or mechanical disruption of the lysosomes. Zhang et al. developed iron oxide MNPs coated with lysosomal protein marker antibodies to specifically accumulate along the lysosome membrane [227]. In this case, the AMF applied (20 Hz, 30 mT) was at a lower frequency where only physical rotations by the nanoparticles would be expected. Thus, it was concluded that the resulting cellular apoptosis occurred due to the lysosomal disruption from the rotational forces. A schematic of magnetic nanoparticle actuated lysosomal membrane permeabilization can be found below in Figure 7a.

Further evidence of lysosomal membrane permeabilization was also observed by Sanchez et al. through iron oxide nanoparticles conjugated with a synthetic replica of gastrin to target CCK2R receptors frequently overexpressed by cancer cell lines [228]. Despite a relatively low heating power from the core nanoparticles and low amount of internalization, the cells with AMF (275 kHz, 40 or 52 mT) exposure displayed lysosome membrane permeabilization followed by the leaking of cathepsin B resulting in cellular death. In follow-up work, the authors fabricated a miniaturized electromagnet to produce an AMF

while cells are studied in real-time using confocal microscopy (Figure 8a) [229]. Within 30 minutes of AMF (300 kHz, 53 mT), the cells displayed elevated reactive oxygen species (ROS) levels and lysosomal permeabilization. Interesting, the lysosomes were influenced by the field and organized in needle-like formations in some cells (Figure 8c,d). Considering the wide variety of assays available, this technology will enable insight into fundamental cellular and molecular mechanisms occurring during treatments.

One example chemical effect is the production of ROS from iron oxide MNPs. In the presence of endogenous hydrogen peroxide, free radicals are generated through Fenton-like chemistry [230, 231]. Free radical generation can result in cellular oxidative stress, which is believed to be one of the key underlying mechanisms of concentration dependent cytotoxicity of iron oxide MNPs [232, 233]. In previous work, Cochran et al. demonstrated that targeted antioxidant nanoparticles of polytrolox were able to suppress ROS generation and protect cells from concentration dependent iron oxide cytotoxicity [234]. One of the interesting questions in this field is whether the source of the Fenton-like chemistry is catalytically driven in a homogeneous or heterogeneous manner (Figure 9a). Voinov et al. have demonstrated through spin-trapping EPR that $\gamma$-$Fe_2O_3$ nanoparticles produce hydroxyl radicals on the surface at a 50-fold increase compared to dissolution of free ions [235]. However, accounting for nanoparticles primarily being internalized into lysosomes, the shift in pH (~4.5) could result in some dissolution of iron oxide to iron ions. These free ions have the potential to leave the lysosome to the cytosol, mitochondria, or endoplasmic reticulum where they would encounter conditions more favorable for Fenton-like chemistry in terms of available hydrogen peroxide [230, 236–239]. While studying the roles of silica coatings for surface passivation, the toxicity of iron oxide nanoparticles were tied to intracellular release of iron ions, which would react with mitochondrial hydrogen peroxide [240]. Limited research has been performed studying the effects of AMF on catalytically driven ROS production from MNPs. Recently, it has been demonstrated that the generation of ROS is enhanced in the presence of an AMF [241]. At nanoparticle concentrations where there was no observable temperature rise, a significant increase in ROS generation compared to the Arrhenius prediction, quantified as an enhancement factor, was observed (Figure 9b). It was hypothesized that the heterogeneous catalytic generation of ROS is accelerated as a result of the local nanoscale heating. In unpublished follow up work, the role of nanoparticle coatings was studied, and the observed results indicated the surface ROS generation was significantly impaired (submitted for publication). One of the coated systems involved glucose functionalization, and it was efficiently internalized into lysosomes and induced significant apoptosis compared to the other nanoparticles, reinforcing the physical or thermal mechanisms discussed above. Despite this study, heterogeneous catalysis coupled with the enhanced reactivity though nanoscale heating is another route of MagMED that needs further investigation.

## 4. Combination therapy

Thermal therapy is often used in combination with conventional cancer therapies such as chemotherapy, radiation, surgical resection, and gene therapy to enhance the efficacy of these treatments. A variety of chemotherapeutics are more effective when administered in the hyperthermia range due to increased rate constants of alkylation, enhanced drug uptake,

and inhibition of repair of drug-induced lethal or sub-lethal damage [27, 242]. When selecting a chemotherapeutic combination therapy, an important consideration is the mechanism of action to make sure that it will complement the hyperthermia modality. When utilizing MMH, chemotherapeutics can either be administered in bulk or bound to the MNPs and released upon exposure to an AMF. Cisplatin (CDDP) [243–246], bortezomib (BZ) [247, 248], and melphalan [249] are common chemotherapeutics that have been studied for bulk combinational treatments with MMH.

Cisplatin binds to DNA, resulting, ultimately, in inter- or intra-strand crosslinking that prevents DNA transcription, blocks cell replication, and finally results in apoptosis. Cisplatin has been previously shown to be more effective when administered in the hyperthermia temperature range [27, 250, 251]. Lee et al. reported the effects of treatment sequence and heating technique (MMH or HWH) on Caco-2 cells [243]. The highest cytotoxicity was observed when CDDP and MMH were applied at the same time with an additional drug exposure period, but MMH was more effective than HWH independent of treatment sequence. The mechanism of cell death after combined treatment is likely to be a form of programmed cell death, such as apoptosis rather than necrosis. In a subsequent study [244], the enhancement of cisplatin in Caco-2 cells by MMH is correlated with an increase is cell membrane fluidity. The presence of copper inhibited CDDP uptake in control cells by hindering copper transporter-mediated active transport, but this same inhibition was not seen in HWH or MMH. Platinum concentration inside cells after MMH was significantly greater than after HWH, which corresponded to the increase in membrane fluidity observed after MMH. Another study by Kruse et al. used crosslinked dextran coated iron oxide MNPs in the presence of an AMF to administer hyperthermia treatment to A549 lung carcinoma in combination with CDDP [245]. Hyperthermia treatment was administered for 30 minutes simultaneously with CDDP and resulted in an additive effect of the combined treatment when analyzed 72 hours post treatment as shown in Figure 10a.

An *in vivo* study of MMH (60 minutes at 43°C) combined with CDDP on murine mammary adenocarcinoma model showed that MMH combined with CDDP was 1.7 times more effective than MMH alone and 1.4 times more effective than CDDP alone [246]. Tumor growth was monitored over time and the control took 14 days to grow three times its original size whereas MMH alone resulted in a delay to 21 days, CDDP alone took 25 days and the combined treatment took 36 days.

Bortezomib (BZ), an inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells, is another chemotherapeutic that has been studied in combination with MMH [247, 248]. Alvarez-Berrios et al. showed that MMH enhances the cytotoxicity of BZ in both BZ sensitive (MDA MB 468 and caco-2) and resistant (A2780) cancer cell lines [247]. Carboxymethyl coated iron oxide MNPs (3.8 mg/mL) in the presence of an AMF (233 kHz) at 29.39 or 34.73 kA/m resulted in hyperthermia treatment at 43°C or 45°C, respectively. A different concentration of BZ for each cell line was used in order to produce approximately the same level of proteasome inhibition after a pre-exposure time of 3 hours. Although BZ sensitive cells and BZ resistant cells showed similar levels of proteasome inhibition, thermal sensitization induced by MMH in combination with BZ in cells resistant

to BZ resulted in significant cell death potentially due to an increase in cell membrane fluidity.

BZ is a drug that increases the toxicity of proteotoxic stress in cancer cells because such cells produce significant amounts of misfolded and non-functional proteins, such that alternative mechanisms of cell protection against proteomic stress can be overwhelmed [248]. Additionally, it has been shown that the combination of cellular effects induced by MMH, such as microtubule disruption and protein damage, results in progressive enhanced proteotoxic stress, which can lead to programmed cell death. MCF-7 cells treated with MMH or MMH and BZ at 43 °C (30 minute recovery time) showed more protein aggregation surrounding the nucleus compared to HWH or BZ with HWH, respectively. After 2.5 hours of recovery time, MMH had induced significant microtubule damage (43°C) as shown in Figure 10b. It was speculated that the combination of microtubule damage and increased protein aggregation caused by MMH induces progressive enhanced proteotoxic stress, which produces significant cell death (Figure 10c).

As previously mentioned, chemotherapeutics can be combined with MMH by functionalizing the magnetic nanoparticle with a chemotherapeutic of interest – by tethering with a responsive linker or encapsulation within a coating matrix – resulting in controlled drug release upon exposure to an external stimuli such as an AMF (as discussed in greater detail in section 2.1 above) or change in pH. Huang et al. recently synthesized pH sensitive cisplatin-loaded magnetite hydroxyapatite nanoparticles [252]. In a low pH environment, 20% of the CDDP was released compared to 5% at a pH of 7. After treatment with the nanoparticles at 300 μg/mL for 48 hours, A549 viability was significantly decreased, and further decreased in the presence of an AMF for 30 minutes resulting in a temperature increase to 43°C. Additionally, in an *in vivo* subcutaneous rat model, tumor growth was completely inhibited in the group treated with the nanoparticle system combined with AMF treatment. In another study by Babincova et al., iron oxide nanoparticles were coated with a hydrophilic starch polymer coupled with phosphate functional groups [253]. The negative coating charge allowed for ionic binding of positively charged species such as cisplatin. A 20 minute hyperthermia treatment was induced using an AMF (3MHz, 1.5 mT), and during this time, almost all of the drug was released from the nanoparticle. The combined MMH and CDDP treatment from the drug loaded iron oxide nanoparticle resulted in a relative viability of 23.6 ± 8.6%. This is significantly less than either the hyperthermia treatment (85.2 ± 7.5%) or the equivalent CDDP treatment (73.8 ± 5.6%) alone, indicating a synergistic toxicity of CDDP and MMH.

5-fluorouracil (5-FU) has also been conjugated to iron oxide nanoparticles for combinational therapy. Li et al. functionalized a magnetite core with PMSA followed by covalent modification with poly-A15 [254]. The nanoparticles were then functionalized with 5-FU and tagged with a HER2 antibody as shown in Figure 11a. A subcutaneous model with a bladder cancer cell line (MBT-2) was used to evaluate the efficacy of combined 5-FU and 15 minute thermal therapy treatment. For small tumors, hyperthermia treatment alone was able to significantly reduce the tumor volume. However, for larger tumors, only the combined treatment of using 5-FU functionalized nanoparticles for MMH resulted in a decrease in tumor volume. A complementary result was seen when the targeted, drug

functionalized nanoparticles were injected through the tail vain followed by AMF exposure. The nanoparticles without AMF treatment did not inhibit tumor growth (likely due to no 5-FU release) nor did treatment with an equivalent dose of 5-FU. The drug loaded nanoparticles with AMF exposure led to complete tumor regression two days after the last treatment (Figure 11b). In another study, 5-FU and curcumin were functionalized to magnetic nanoparticles, and when exposed to an AMF, the dual drug release combined with thermal therapy led to an enhanced efficacy compared to either drug treatment alone [255]. This is thought to be due to increased efficiency of drug diffusion from the nanoparticles or that injured cells could not recuperate from the impairment induced by thermal treatment owing to the combined treatment of 5-FU and curcumin.

Heat shock protein (HSP) inhibitors are of particular interest due to up regulation of heat shock proteins during hyperthermia treatment. Geldanamycin, a HSP 90 inhibitor, was conjugated to iron oxide nanoparticles via a thermally cleavable linker for controlled release upon exposure to an AMF [256]. An *in vitro* study on MDA MB 231 cells showed geldanamycin functionalized iron oxide MNPs negated the increased HSP 90 expression seen with MMH alone, and an *in vivo study* resulted in complete tumor regression 8 days after treatment when the geldanamycin functionalized MNPs were used for MMH.

Additional studies have been completed using methotrexate [257], doxorubicin [258], and erlotinib [258] functionalized magnetic nanoparticles for combinational therapy. These studies also indicate that drug combined with hyperthermia via MNPs in an AMF is more effective than either treatment alone. Methotrexate combined with MMH resulted in a synergistic treatment of MCF-7 cells *in vitro* [257] while doxorubicin efficacy was significantly increased when combined with MMH [258].

MMH can also be combined with radiation and gene therapy for enhanced efficacy. There are several studies that address hyperthermia combined with radiation [259–261], but minimal studies that utilize MMH with radiation therapy. Hyperthermia has been shown to increase blood supply to the tumor, which increases the local oxygen levels and the efficacy of radiation therapy is tied to the formation of free radicals more so than DNA damage. In an orthotopic tumor model of R3327 Dunning tumor cell line, MNPs with an aminosilane shell were used for two rounds of MMH for 30 minutes each combined with 20 Gy, 40 Gy or 60 Gy total radiation therapy [262]. Thermal therapy viability inhibition alone was 44.1–51.7% whereas the combined treatment (20 Gy radiation total with hyperthermia) had an inhibition of 87.5–89.2% compared to the control. A clinical trial was also completed in which 59 patients with recurrent glioblastoma received a direct injection of iron oxide MNPs followed by 30 minutes of heating (43°C) in an AMF (100 kHz, 2–15 kA/m) [263]. A median radiation dose of 30 Gy was given to the patients immediately before or following hyperthermia treatment. The combined therapy resulted in an extension of the median overall survival after primary tumor diagnosis from 14.6 to 23.2 months. There was also a gain of 7.2 months for survival following tumor recurrence. Although there are differences between the treatments of the patients, the increase in survival time can be attributed to the combination of thermo-radiotherapy.

Thermal therapy via magnetic nanoparticles combined with gene therapy is a recently developed area in this field. A review of heat responsive gene expression utilizing thermal therapy via other methods than MNPs was published in 2009 [264]. More recently in 2014, Shah et al. evaluated the efficacy of pro-apoptotic amphipathic tail-anchoring peptide (ATAP) delivery by MNPs. MMH was used to increase pro-apoptotic proteins in glioblastoma multiforme cells and metastatic breast cancer cells, while the ATAP peptide selectively targets mitochondria and induces cytochrome c release through disruption of the mitochondrial membrane. The result of gene therapy treatment combined with MMH resulted in enhanced toxicity compared to ATAP therapy alone, which is likely due to an increase in peptide solubility upon conjugation to the nanoparticles. In another study completed by Yin et al. in the same group, lethal-7a miRNA was conjugated to MNPs, as lethal-7a is a known tumor suppressor that inhibits malignant growth by targeting factors such as the BRCA family, RAS, IGF1R and c-Myc, which all overlap with downstream regulation of heat shock proteins [265]. Combined thermal therapy via MMH and gene therapy with lethal-7a showed an additive effect, resulting in significantly more apoptosis in brain cancer cells than either treatment alone. Overall, gene therapy combined with MMH is a promising avenue for combinational therapy and can potentially result in more personalized treatment of cancer.

## 5. Conclusions and future perspectives

MNPs and their composites have been applied in various strategies for controlled drug delivery. For temporal control, novel macroscale materials and systems have been developed where AMF-triggered thermal transitions resulted in modulated release of a drug. These thermal transitions have included, among others, swelling transitions of thermoresponsive polymers, glass transition temperature and phase transitions of lipid matrices. In addition to these thermal transitions, various groups have explored ways to achieve modulated release using a static or low frequency magnetic field, where there is minimal or no heating effect. These systems have utilized the magnetic field-induced mechanical deformations to modulate release through solvent expulsion, decreased diffusivity, etc. At the micro- and nano-scale, temporal control has been demonstrated using both thermal effects and mechanical effects induced by AMFs of various frequencies and amplitudes. Nanoparticle platforms including, but not limited to, liposomes, polymersomes, and polymer micelles, have been studied and demonstrated to have modulated release of drugs in the presence of an AMF. In addition to the temporal control, there have been multiple examples of enhanced treatment due to the magnetic guidance of delivery systems for localized delivery at stents, in tumors, and in specific regions such as the lungs through pulmonary delivery. Although there have been various *in vivo* demonstrations of efficacy, these therapeutic approaches have not translated to the clinic as of today. With the further development of MNPs and these composite systems, there are great expectations and promise for these remote controlled drug delivery systems to impact the treatment of various diseases where pulsatile release or other modulations in therapy over an extended period of time is required.

Thermal therapy using MNPs has been shown to decrease cancer cell growth both *in vivo* and *in vitro* to a greater extent than thermal therapy administered by external methods such as HWH. In addition, immunotherapeutic effects of thermal therapy have been observed and

show promise for future development. However, due to the bulk concentration of nanoparticles required to heat tissue into the hyperthermia range and the lack of development of magnetic fields to penetrate deep into the body, translation to clinical trials has been minimal. Additionally, applications of MMH as a viable treatment modality is limited by tumor size due to heat transfer from small tumors (i.e. metastases) to the surrounding tissue. In order to improve thermal therapy via MNPs, *in vivo* heating properties need to be improved and specific targeting to tumor tissue to decrease non-specific accumulation need to be developed.

Energy delivery on the nanoscale provides another avenue of thermal therapy where only intracellular nanoparticles are actuated by an AMF, resulting in subcellular heating effects without a macroscopic temperature rise. Energy delivery on the nanoscale has been shown to result in destabilization of lysosomal membranes and toxic effects to other organelles. Previously, the focus of MNP development was improving the heating capabilities to overcome the thermal delivery limitations, but in addition to this need for other therapy strategies, many researchers are now exploring intracellular targets for nanoscale thermal therapy applications. Further studies need to be performed to gain a better fundamental understanding of the mechanisms at play. However, an exciting prospectus is to combine the knowledge gained through combined chemotherapy with this new therapy strategy. Novel nanoparticle architectures should be synthesized to deliver therapeutics intracellularly, relying on nanoscale thermal effects to improve efficacy.

Thermal therapy as a single treatment is often insufficient to induce irreparable cellular damage, but when combined with a secondary treatment, the combinational therapy is often found to be more effective than either treatment alone. A variety of chemotherapeutics are more effective when administered at elevated temperatures due to increased rate constants of alkylation, increased drug uptake, and repair inhibition of drug-induced lethal or sub-lethal damage. Thermal therapy also increases oxygen content within tissue, making radiation more effective. Therefore, as a combinational treatment, thermal therapy via MNP activation in an AMF has greater application. However, the same limitations such as concentration dependence, heating properties, and AMF parameters still remain. As the field progresses, it will be important to develop targeted MNPs with excellent heating properties in order to overcome some of these limitations and, as previously mentioned, explore nanoscale thermal therapy in combination with conventional treatments.

In the last several years, there have been many exciting developments in the use of MNPs and their composites for remote controlled therapies. These include novel remote controlled drug delivery systems at various scales for modulated release and magnetic field guidance, controlled energy release for thermal therapy and nanoscale energy therapy, and thermal therapy in combination with other treatments such as chemotherapy or radiation. With numerous *in vivo* demonstrations of efficacy, these remote controlled therapies are starting to progress to the clinic, and they are expected to greatly impact the treatment of various diseases in the future.

## Acknowledgements

AKH, RJW, and NAS were partially supported by Grant Number R25CA153954 from the National Cancer Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health. Additionally, AKH was partially supported by the National Science Foundation Graduate Research Fellowship Program Grant No. DGE-1247392. Any opinions, findings, and conclusions or recommendations expressed in this material are those of the author(s) and do not necessarily reflect the views of the National Science Foundation.

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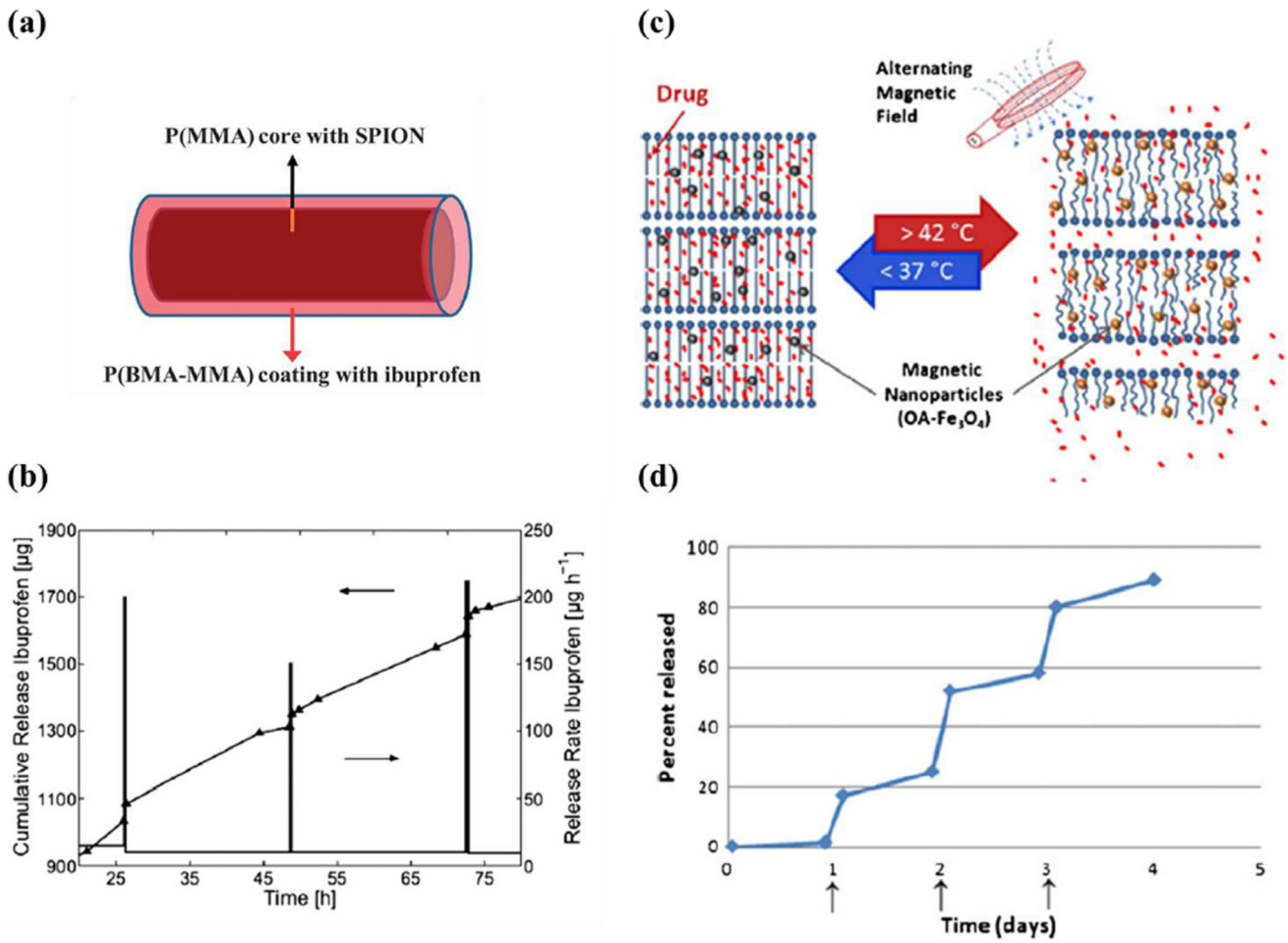



**Figure 1.**

In (a), the core–shell implant design is schematically depicted, and in (b), on-demand release from a single implant with a high ibuprofen loading (29 wt%) and a core containing 50 wt% of iron oxide particles in a 37°C bath exposed to the magnetic field for 15 minutes [54]. In (c), a schematic illustration of the proposed concept of monoglyceride-based thermoresponsive drug delivery system [55]. In (d), AMF triggered in vitro release of nifedipine from GMO-GMS (75:25 wt%) matrix. The arrows indicate the exposure of the matrix to AMF for 5 minutes.

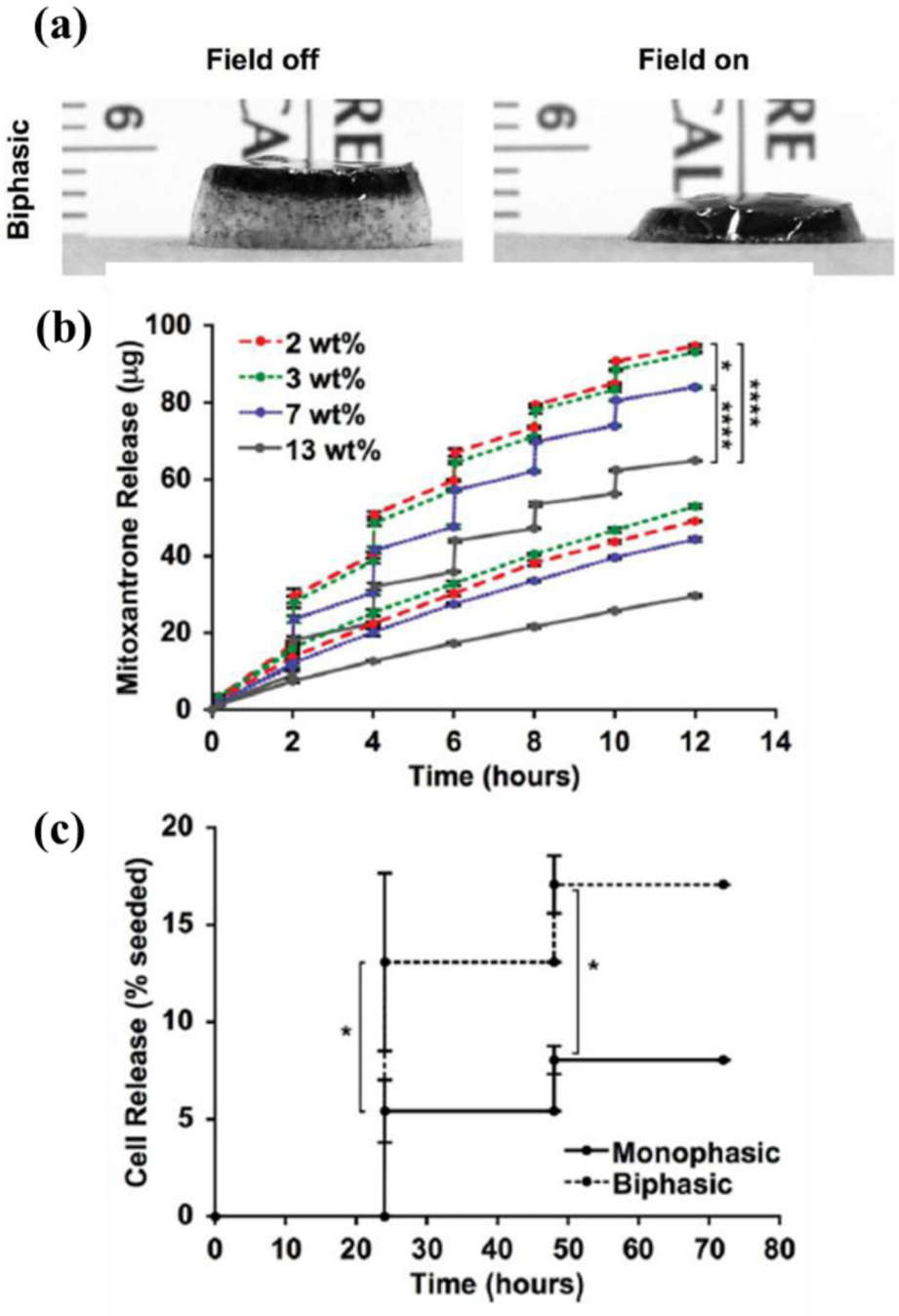



**Figure 2.**

In (a), photographs of small 7 wt% iron oxide biphasic ferrogels in the presence of no magnetic field (field off) and a moderate vertical magnetic field gradient (field on). In (b), mitoxantrone release from biphasic ferrogels following no stimulation (bottom curve) or magnetic field stimulation (top curve). All ferrogels were initially loaded with 150 μg mitoxantrone. In (c), viable cell release from biphasic ferrogels, viable cells were defined as cells excluding trypan blue. Taken with permission from [68].

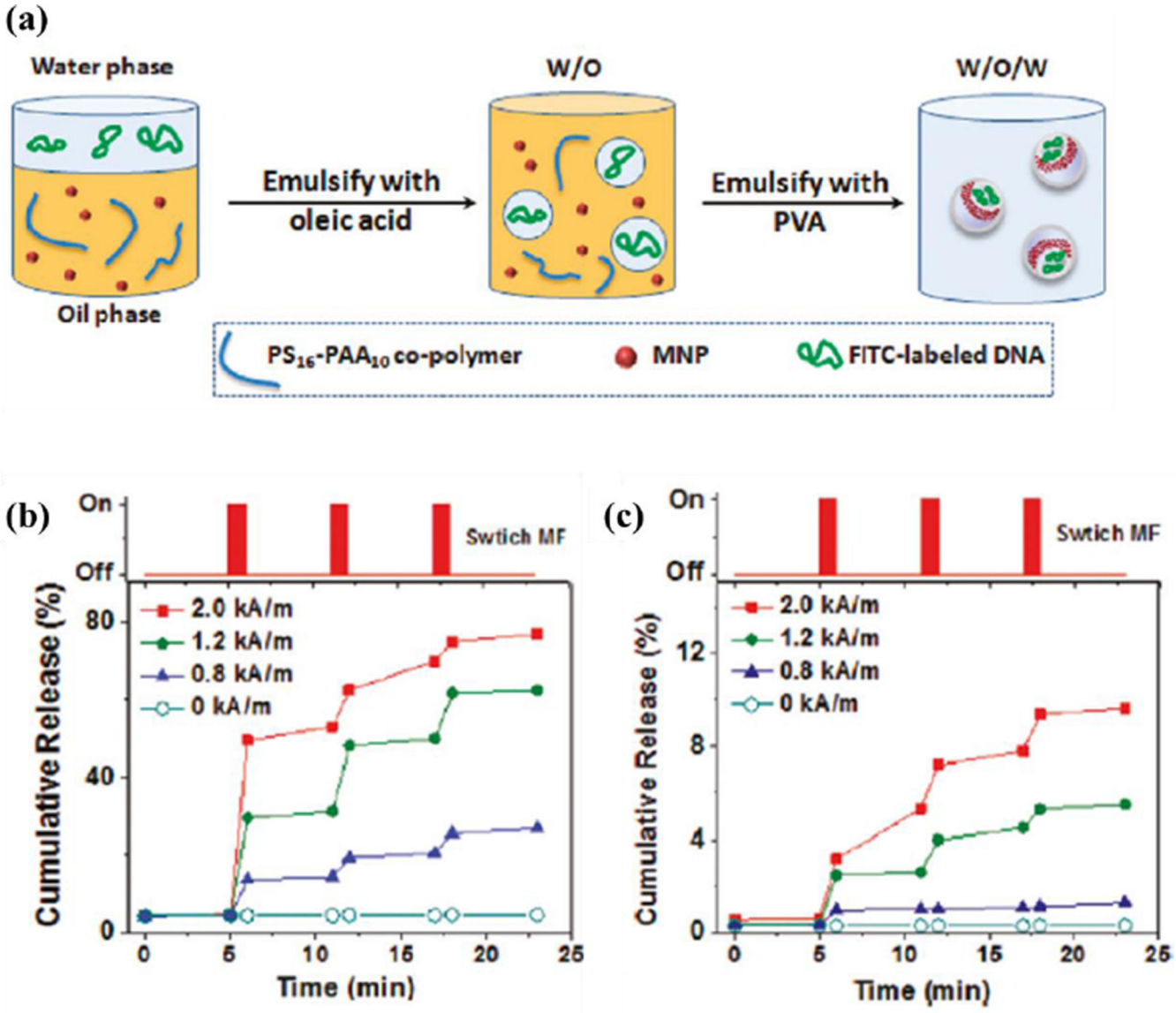



**Figure 3.**

In (a), schematic illustration of the key steps in nanocapsule preparation. In the first step (W/O emulsion), an aqueous solution of hydrophilic compounds is emulsified in a volatile organic solvent with oleic acid as the surfactant, followed by the second round emulsion (W/O/W) with PVA as the surfactant. In (b), AMF-induced DNA release from nanocapsules. During the short experiment period, DNA release is negligible without magnetic field triggering (black curve). The release rate can be significantly increased if AMF is applied. When the pulsed magnetic field is set at 0.8 or 1.2 kA/m (blue and green), the NCs release DNA in a burst-zero-burst fashion. When the pulsed field strength is increased to 2.0 kA/m (red), DNA release is enhanced when the field is on and becomes appreciable even when the field is turned off. In (c), cumulative pyrene release profiles in the absence or presence of AMF. The overall trends for hydrophobic compound release with or without HFMF are similar to those for hydrophilic compounds, but the total amounts released are significantly less. Taken with permission from [115].

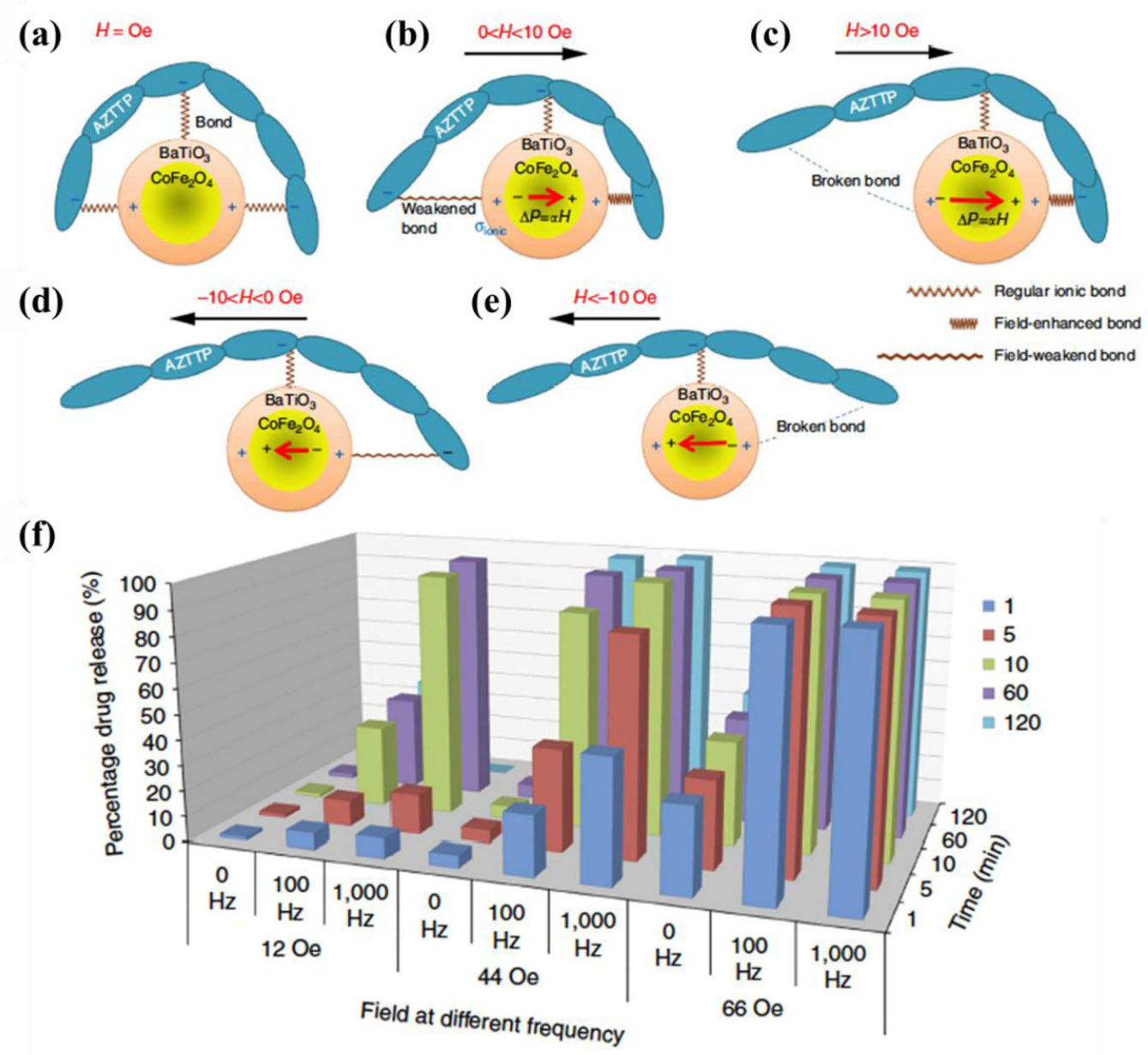



**Figure 4.**

In (a)–(e), A simplified (one directional) illustration of the concept of on-demand drug release stimulated by a uniform alternating current magnetic field in X direction. (a) At zero field, only the ionic charge is present in the magneto-electric nanoparticle shell. (b) An additional dipole moment (proportional to the magnetic field) breaks the original symmetry of the charge distribution in the shell. (c) As the field is increased above the threshold value, the bond on one side is broken. (d,e) The field is reversed to break the bond on the opposite side of the nanoparticle. The red arrows show the electric dipole due to the magneto-electric effect. In practice, owing to the random configurations of nanoformulations with respect to the field, the effect is present along every central bond orientation. In (f), pharmacokinetics study: three-dimensional chart representation of the drug release percentage at various

combinations of the field amplitudes (12, 44 and 66 Oe), the frequency (0, 100, and 1,000 Hz) and the treatment duration (1, 5, 10, 60 and 120 min). Taken with permission from [137].

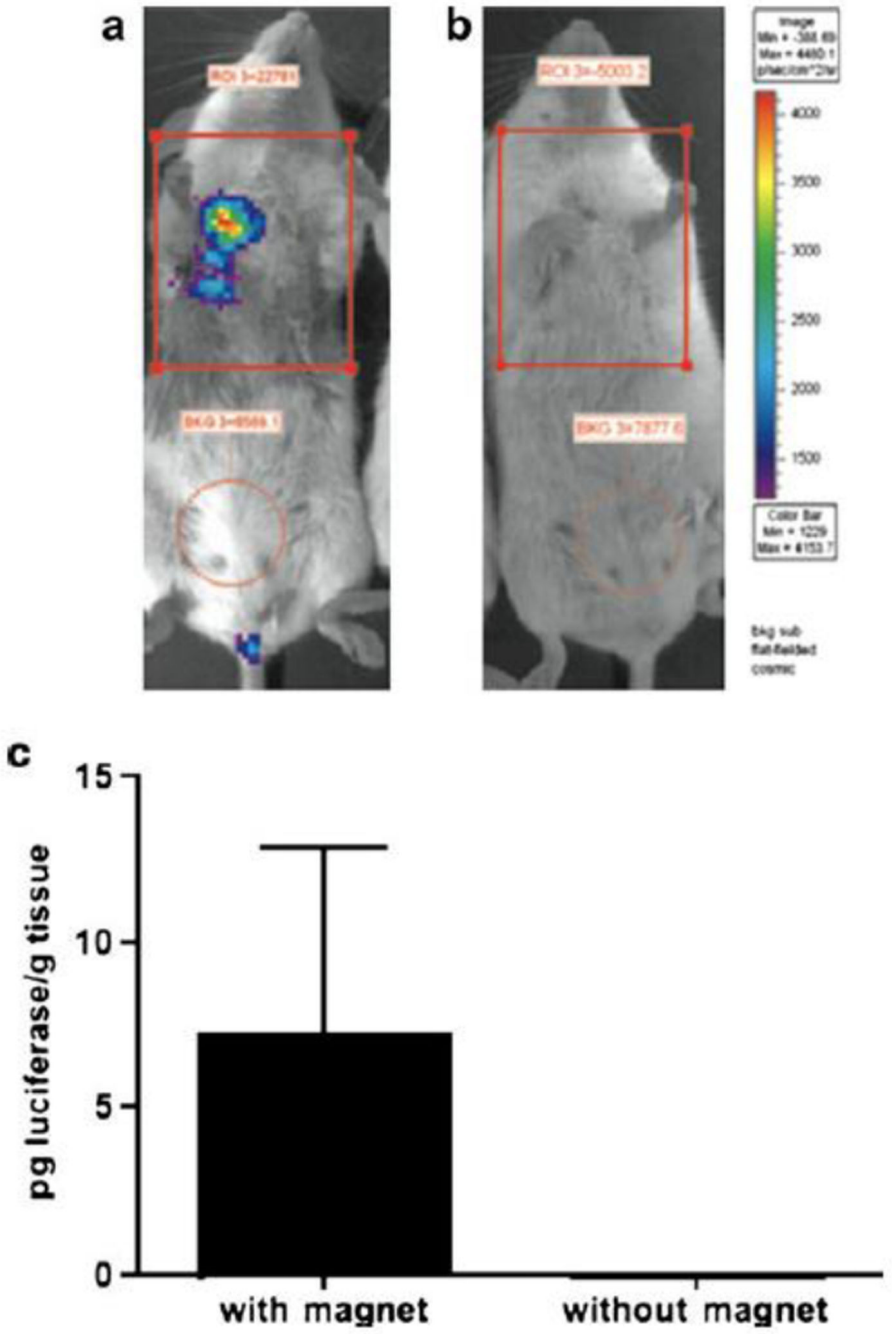



**Figure 5.**

A nanomagnetosol solution comprising PEI-pDNA gene vectors coding for the luciferase gene and SPIONs was nebulized to Balb/c-mice (n03) either with (a) or without (b) an external magnetic gradient field applied to the right chest. Twenty-four hours after nebulization luciferase activity in the lungs was measured using in vivo bioluminescence imaging in mice. The lungs were removed subsequently to conduct an ex vivo luciferase assay, revealing a mean luciferase expression of 7.2 pg luciferase per gram tissue in mice

that had been exposed to a magnetic gradient and no luciferase in mice without a magnetic gradient during the nebulization procedure (c). Taken with permission from reference [164].

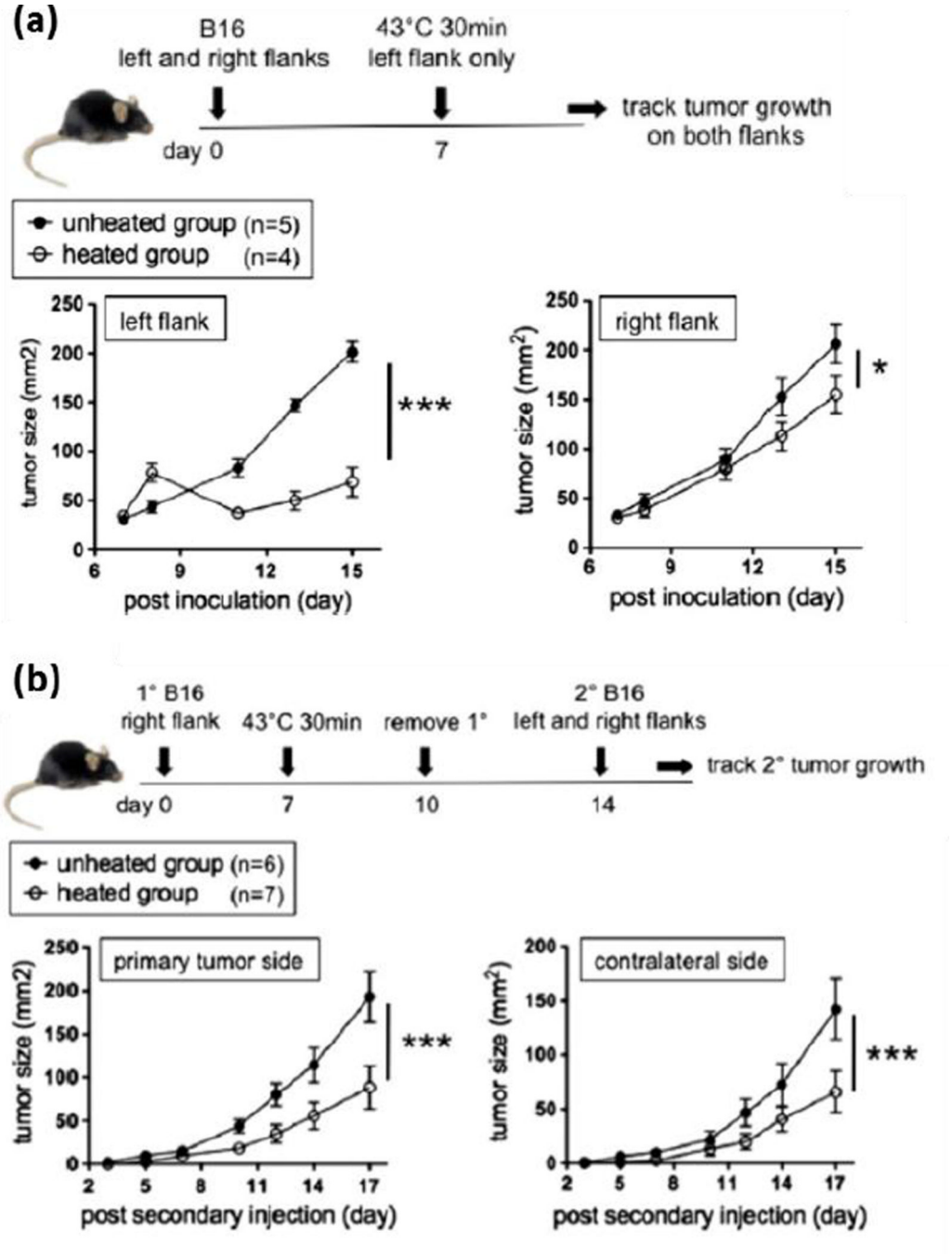



**Figure 6.**

Local hyperthermia using magnetic nanoparticles in an AMF for 30 minutes at 43°C on the left flank B16 tumor slows B16 tumor growth on the right flank (a). Local hyperthermia using magnetic nanoparticles in an AMF for 30 minutes at 43°C on B16 primary tumors slows secondary B16 secondary tumors on both the primary tumor side and contralateral side (b). Taken with permission from reference [198].

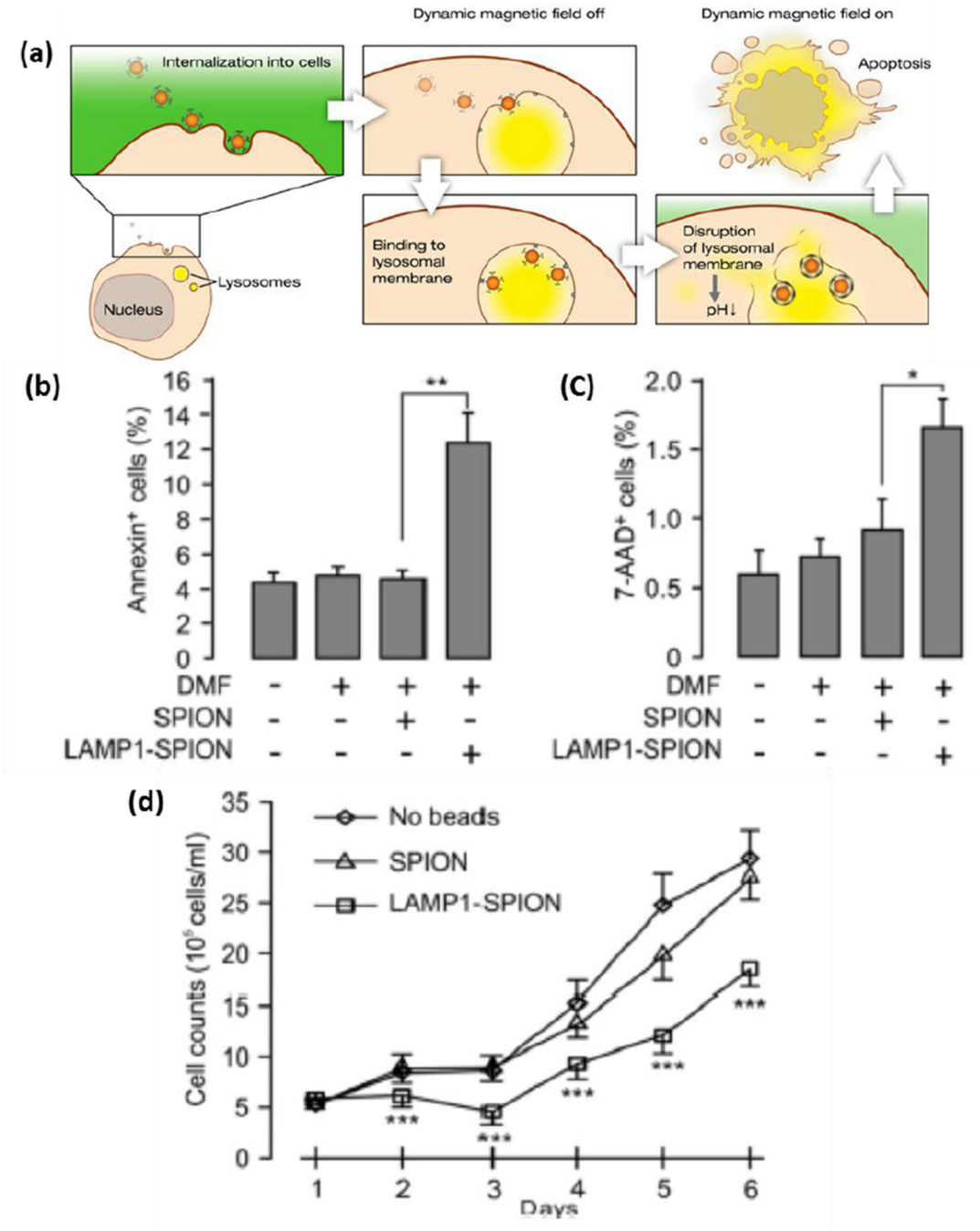



**Figure 7.**

(a) Schematic of envisioned route of MagMED therapy through apoptosis triggered by lysosomal membrane permeabilization. Targeted nanoparticles would circulate the body until coming into contact with cancer cells. The targeting ligand binds to the respective cell marker and the nanoparticles are internalized by the cell entering lysosomes. When the AMF is turned on the nanoparticles are actuated and the energy delivered disrupts the lysosomal membrane spewing the contents inducing apoptosis. Early (b) and late (c) stage apoptosis respectively were detected by the number of annexin V and 7-AAD positive cells to the

number of HOECHT stained cells. (d) Decreased rate of cell growth observed after treatment with LAMP1-SPOINs and AMF exposure. Taken with permission from reference [227].

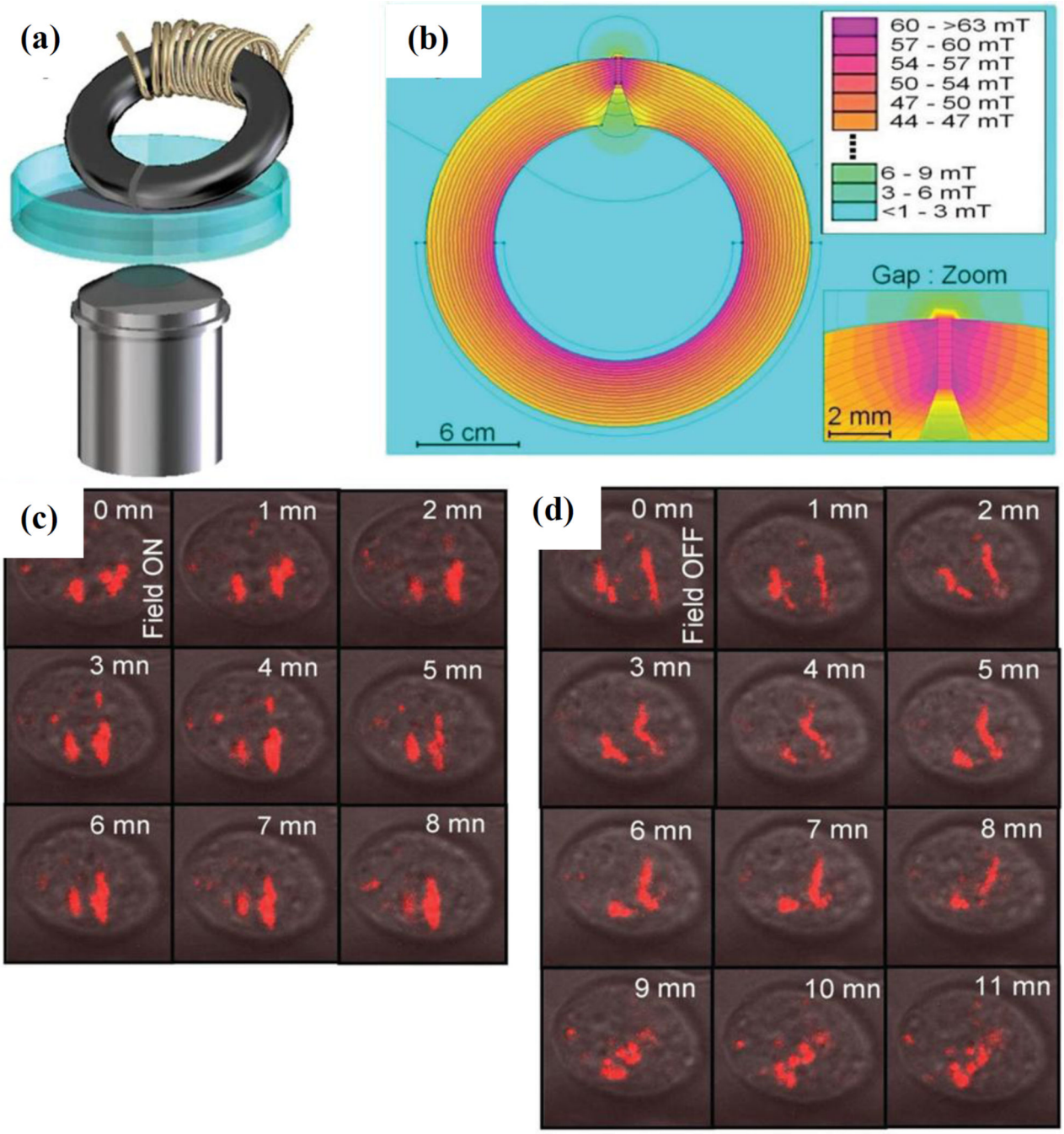



**Figure 8.**

Schematic of the miniature electromagnet placed on the confocal microscopy stage (a). Magnetic field map modeled using finite element method magnetic software with the insert enlarging the field surrounding the V-shape gap fabricated to prevent shadowing (b). When the field is activated, internalized nanoparticles induce alignment of the lysosomes (c) that is reversible when the field is turned off (d). Taken with permission from reference [229].

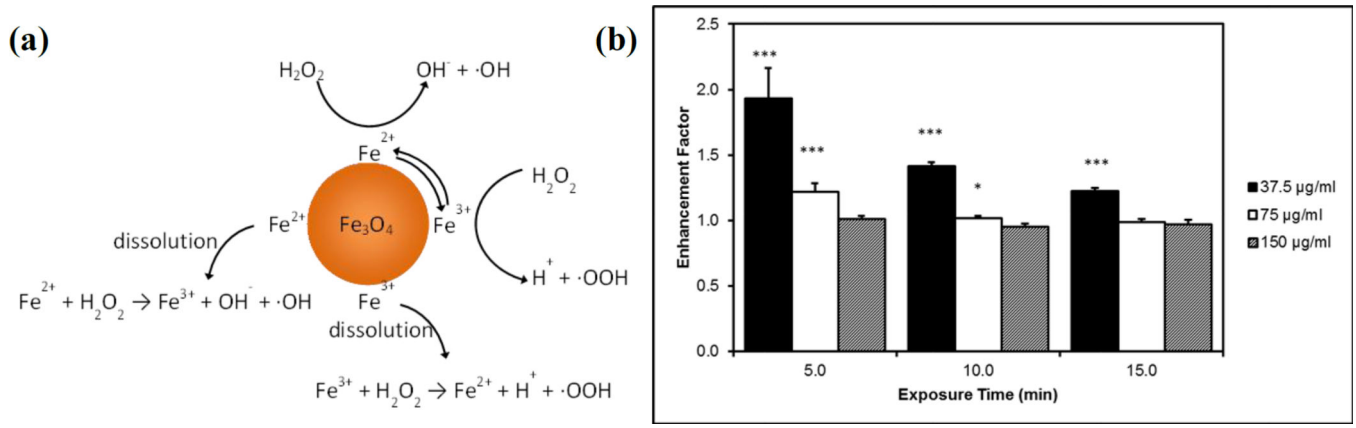



**Figure 9.**

Schematic of the Fenton-like generation of free radicals by iron oxide nanoparticles (a). Enhancement factor, defined as the ratio of experimental methylene blue degradation versus the Arrhenius prediction at steady state temperature with AMF exposure, at different iron oxide concentrations and reaction time (b). Enhancement decrease over time was attributed to field induced agglomeration. Taken with permission from reference [241].

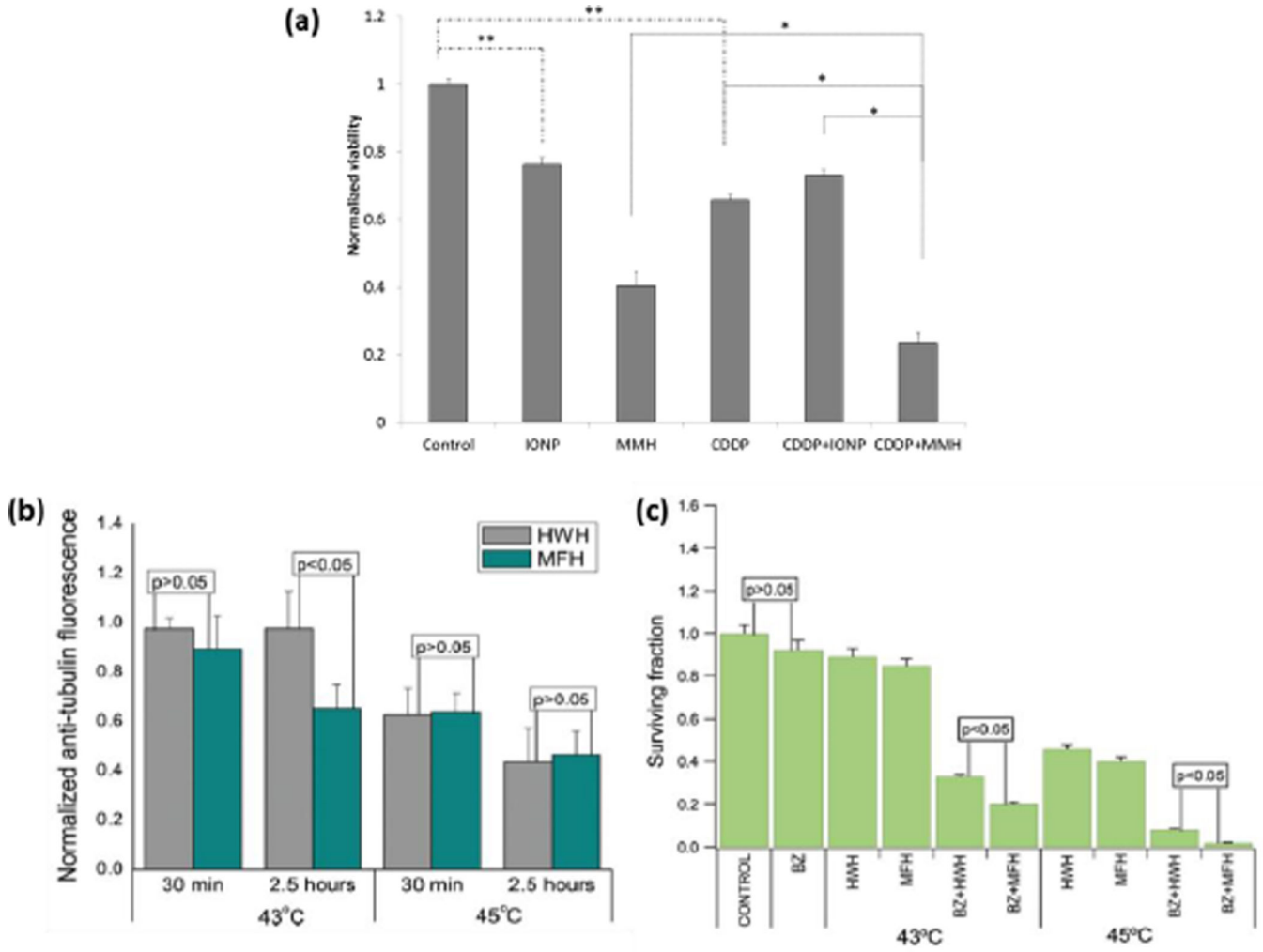



**Figure 10.**

(a) Magnetically mediated hyperthermia in combination with cisplatin (CDDP) for 30 minutes significantly decreases the viability of A549 lung carcinoma to a greater extent than either treatment alone [245]. (b) Microtubule damage due to hot water hyperthermia (HWH) or magnetic fluid hyperthermia (MFH) at 43°C or 45°C [248]. (c) The surviving fraction of MCF-7 cells treated with HWH or MFH with or without 100nM bortezomib (BZ), with MFH being more effective than HWH in combination with BZ [248].

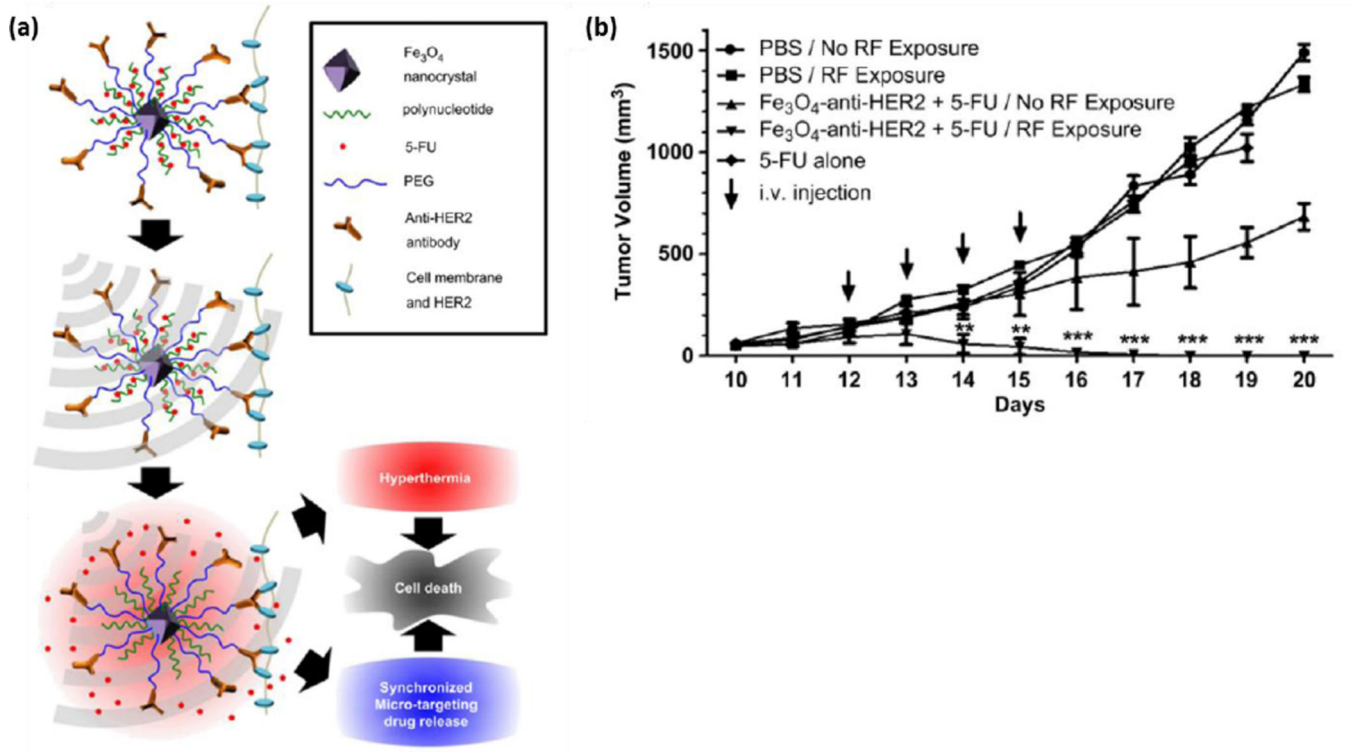
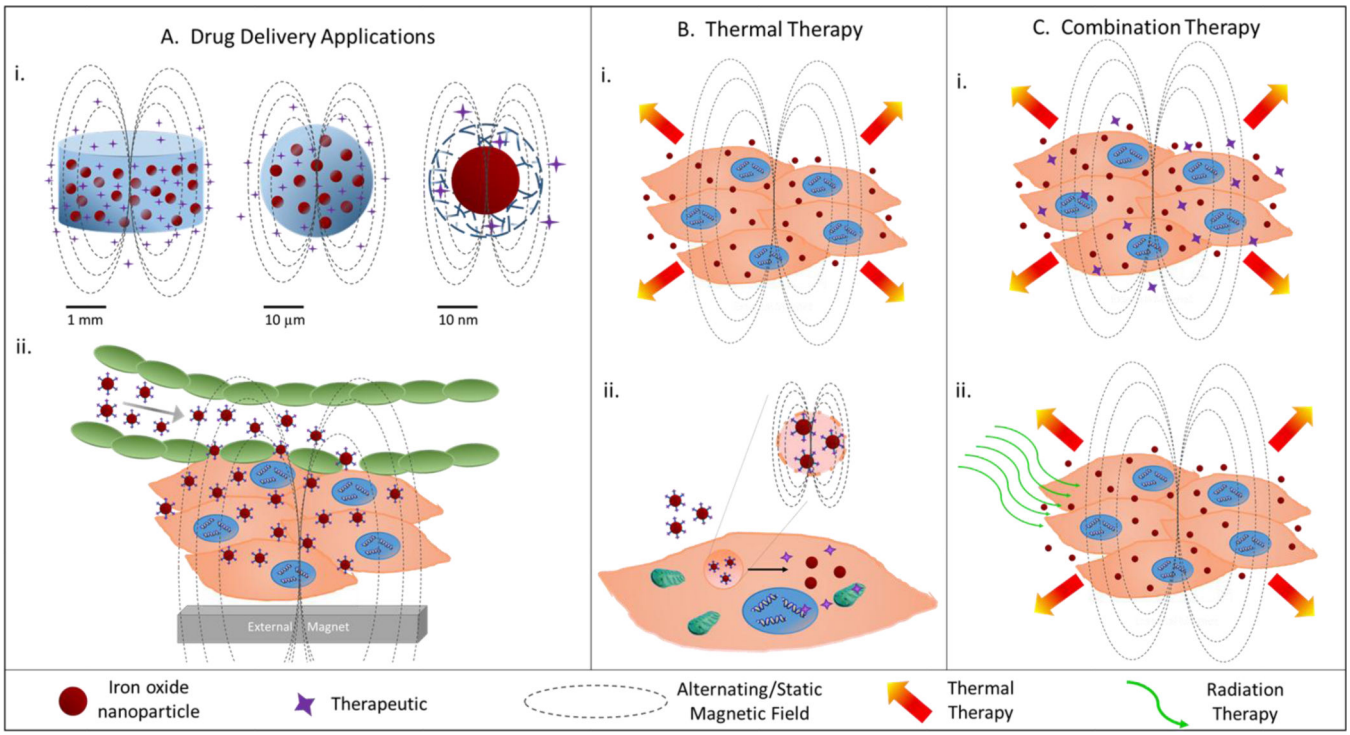



**Figure 11.**

(a) Schematic of iron oxide nanoparticles coated with a polynucleotide and PEG, then functionalized with 5-FU and anti-HER2 antibody for localization at the cell membrane. Upon activation by an AMF, 5-FU is released from the nanoparticle and thermal therapy is induced so that both hyperthermia and synchronized micro-drug release lead to cell death. (b) Tumor volume of tumors treated with magnetically mediated hyperthermia using 5-FU functionalized nanoparticles which were targeted to HER2 grew significantly slower than the other treatments. Taken with permission from reference [254].




**Schematic 1.**

This review highlights the uses of MNPs for controlled release therapies. A) Drug delivery applications are divided into i) controlled drug release from a system containing MNPs upon exposure to an alternating or static magnetic field and ii) magnetic guidance. B) Thermal therapy can be remotely controlled for i) local applications or ii) nanoscale heating applications. C) Thermal therapy is often administered in combination with a secondary treatment such as i) a therapeutic or ii) radiation.