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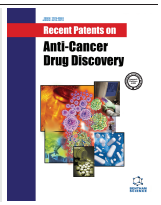
REVIEW ARTICLE

Developing Antitumor Magnetic Hyperthermia: Principles, Materials and Devices



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Abstract: ***Background and Objective:*** Methods of local or loco-regional anticancer treatment are of the utmost importance because the therapeutic 'power' is applied directly to the disease site. Consequently, general toxicity is minimized. Hyperthermia, that is, a sustained increase of intratumoral temperature up to 45°C, has been investigated as a perspective treatment modality alone and/or in combination with ionizing radiation or chemotherapy. Still, the surrounding tissues can be damaged by the external heat.

Method: Development of new materials and devices gave rise to methods of inducing hyperthermia by a high frequency magnetic or electromagnetic field applied to the tumor with exogenous nanosized particles captured within it. The idea of this approach is the release of local heat in the vicinity of the magnetic nanoparticle in a time-varying magnetic field due to transfer of external magnetic field energy into the heat. Therefore, tumor cells are heated whereas the peritumoral non-malignant tissues are spared.

Results: This review analyzes recent advances in understanding physical principles that underlie magnetic hyperthermia as well as novel approaches to obtain nanoparticles with optimized physico-chemical, toxicological and tumoricidal properties. Special focus is made on the construction of devices for therapeutic purposes.

Conclusion: The review covers recent patents and general literature sources regarding magnetic hyperthermia, the developing approach to treat otherwise intractable malignancies.

Keywords: Hyperthermia, magnetic nanoparticles, therapeutic combinations, treatment, tumors.

INTRODUCTION

Hyperthermia is a perspective method of cancer treatment comprising the exposure of the whole body, its local areas or tissues to higher temperatures in order to damage cancer cells. Two different approaches to hyperthermia heating include (a) hyperthermia characterized by temperatures between 41-45ºC, and (b) thermoablation when temperature rises higher than 45ºC for the local induction of tissue necrosis [1].

Various techniques and methods of hyperthermia include local hyperthermia, regional hyperthermia and whole-body hyperthermia. The latter can be induced by endogenous or exogenous heat sources and usually heats the entire body to ~39-43ºC [1, 2]. This modality is typically used to treat distant metastases [1, 3]. Regional hyperthermia affects a body area or an entire organ. Usually, the goal is to sensitize tumor cells to other therapies such as radiation and chemotherapeutic drugs [3]. Methods of local hyperthermia comprise the administration of ferromagnetic or metal particles to the tumor area followed by exposure to a magnetic or electromagnetic field: HF, UHF, SHF, constant magnetic field, etc. This array of local hyperthermia methods is called magnetic fluid hyperthermia (MFH) or simply magnetic hyperthermia (MH).

In general, the main problems associated with currently available methods for inducing hyperthermia include the necessity to localize the treatment to the target site and to maximize heating within the diseased tissue while sparing the surrounding normal one [2]. The main disadvantages of particle-based methods of hyperthermia comprise possible overheating (the exact duration should be calculated), toxicity of formulations, complications of selective delivery to the application area, non-uniform distribution of magnetic particles across the tumor, and an expensive equipment. Therefore, development of new efficient methods of treatment by means of MH must address the above-mentioned issues. In this review we discuss recent developments of MH methods, focusing mainly on physico-chemical properties of particles and device engineering. Other important aspects such as the modes of tumor cell death in response to MH and clinical

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settings remained largely beyond the scope of the present study.

PARTICLES, NANOPARTICLES, DELIVERY SYSTEMS AND CARRIERS FOR MH

Magnetic nanoparticles (MNPs) are used in a variety of biomedical applications including contrasting agents for magnetic resonance imaging (MRI), carriers for drug delivery, and heat source for hyperthermia [4]. MNPs possess unique properties such as magnetic transportation, magnetic isolation, and self-heating in an AC magnetic field [5]. The use of MNPs as minimally invasive agents has been introduced by Gilchrist *et al*. in 1957 giving rise to MH [6]. Being subjected to an AC magnetic field, magnetic nanoparticles show remarkable heating effects related to energy losses during the process of magnetization reversal of particles [7]. Besides the opportunity of a precisely localized heat generation, the application of MNPs offers self-limitation of temperature enhancement by using a magnetic material with the suitable Curie temperature [7]. One of the main challenges concerning the application of magnetic nanoparticles in MH is that the heat release should be the highest achievable with the smallest amount of particles (in order to minimize their tentative toxicity).

Nanoparticles can be divided into multi-domain MNPs (>~40nm) depending on the magnetic field parameters and single domain nanoparticles or 'superparamagnetic nanoparticles' with diameters <~40nm. Two different mechanisms are responsible for the delivery of heat in respect to each type. In case of the multi-domain MNPs heat is delivered by displacements of the domain wall (hysteresis losses) [1]. Single domain particles induce heating as a result of loss processes during the reorientation of magnetization in the magnetic field, or frictional losses where the nanoparticle is able to rotate in the surrounding medium [1, 8].

A wide range of currently synthesized MNPs includes metal-based (Fe, Co, Ni), ferrite-based ($MgFe_2O_4$, CoPt, MnAl, $CoFe_2O_4$, etc.) and iron oxide nanoparticles. The latter, despite their relatively weak magnetic properties, are used in biomedicine as hyperthermia agents due to the low toxicity and stable magnetic characteristics. However, Fe_3O_4 nanoparticles are susceptible to phase change into α-Fe_2O_3, γ-Fe_3O_4 or Fe_3O_4 crystals depending on surrounding conditions, and heat generation characteristics and magnetic properties of nanoparticles are thus changed, limiting clinical application [9]. Furthermore, although Co, Ni or Mg-based nanoparticles also have been studied they cannot be applied to the body due to a low heat generation temperature (Co: 25°C, others below 25°C). Therefore, there is a need for nanoparticles applicable as new highly functional hyperthermia agents.

The following parameters should be taken into account in the development of nanoparticles for MH:

- Size, shape;
- Toxicity and biocompatibility;
- Suitability for surface modification;
- Synthesis complexity and reproducibility;
- Heat dissipation (specific absorption rate; SAR);
- Required external magnetic field and reaction rate on the field impact;
- Cost.

A key important parameter in the design of MNPs for MH is SAR [6, 10] that quantitatively reflects the efficiency of MNP colloids to transform magnetic energy into heat. This parameter is defined as the absorbed power normalized by the mass of MNPs, under an applied alternating magnetic field of a certain frequency and intensity H_0 [6]:

SAR = *Absorbed power / Mass of MNPs*.

SAR is a crucial parameter affecting the tissue temperature during MH treatment. Overheating may result in a serious damage to the surrounding cells and an uncontrolled necrosis. On the contrary, the desired therapeutic effect cannot be achieved if the temperature rise is not high enough. SAR in MNPs strongly depends on frequency and intensity of the applied magnetic field as well as on chemical, physical, and magnetic properties of the material [6].

MNPs can be injected intravenously and transferred to specific parts of the body with enhanced permeation and retention effect (EPR) and a magnetic field [5]. Otherwise MNPs can be administered intratumorally (Fig. (**1**)). The tumor is then exposed to the heat generated by MNPs under an external AC magnetic field. The temperature of MNPs is controlled by the strength and frequency of the external magnetic field [5]. Apparently, it is plausible to achieve the temperature enhancement with a smaller amount of MNPs [7].

In order to apply MNPs in therapy it is significant to keep their biocompatibility, avoid aggregation (for EPR effect) and reduce the chance for obstruction of blood capillaries [5]. Continuous efforts have been made to increase SAR and to reduce the dose of nanoparticles, treatment duration as well as side effects [11]. Some of these improvements are discussed below.

The patent literature analyzes superparamagnetic or stable ferromagnetic particles/materials with increased biocompatibility, protective coating and improved heating properties and stability, as well as methods for producing the mentioned materials (Table **1**).

A method of obtaining nanoparticles comprised of iron oxide and silicon-containing casing, and having the SAR value 10-40W per g of Fe with field strength 4 kA/m and frequency of alternating magnetic field 100kHz, has been described in [12]. The invention makes it possible to get biocompatible magnetic particles with high SAR for hyperthermia.

A method of maghemite nanoparticle preparation [13] allows for obtaining a supermagnetic powdered composition which consists of maghemite and a protective coating, that is, an adsorbed growth regulating agent for nanoparticles. The invention simplifies preparation of maghemite nanoparticles and increases chemical stability of supermagnetic spherical nanoparticles (<10nm). These maghemite nanoparticles can be perspective for both hyperthermia and drug delivery.

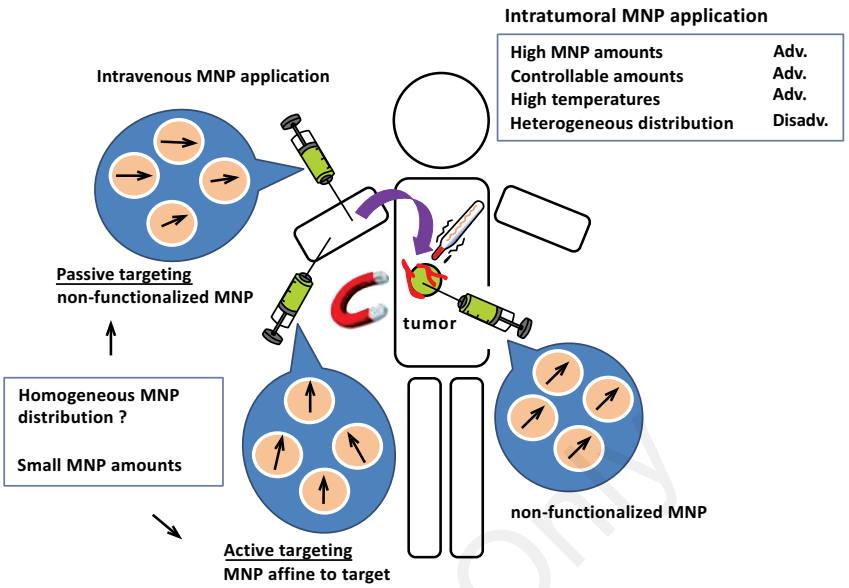

Fig. (1). Application routes in MH [1].

Table 1. Main Characteristics of Described Materials/Particles.

Cited Document	Material/Particles	Size	Modifications	Possible Use
CN104667277 (**2015**)	Iron oxide	-	The surface of the magnetic nanoparticle core is coated with protein to form stable magnetic hydrosol	Hyperthermia, chemotherapy
EA201391119 (**2014**)	Fe, Ni, Co, Gd or their oxides	1-100nm	Nanoparticles are encapsulated in thermosensitive liposomes	Hyperthermia, drug delivery, MRI
EP2377811 (**2011**)	Ferrite ($MgFe_2O_4$, $MgZnFe_2O_4$, or $MgMnFe_2O_4$, etc.)	< 10nm	Nanoparticles engineered by magnesium doping	Hyperthermia
GB2415374 (**2005**)	Iron oxide	5-150nm	Gold core shell; a delivery system may have a biologically active substance bound to the surface of the gold shell of the nanoparticle or contained within the gold shell	Hyperthermia, drug delivery, MRI
JP2013256405 (**2013**)	$Ni_{(1-i)}Zn_iFe_2O_4(0,2 \leq i \leq 0,6)$	10-20nm	A shell comprises amorphous SiO_2 for covering the magnetic nanoparticle core	Thermotherapy
RU2437890 (**2011**)	Metal oxides (Fe, Co, or their alloys)	1-200nm	Nanoparticles form stable complexes with bifunctional compounds (thiols, carboxylic acids, hydroxamic acids	Hyperthermia, drug delivery, MRI
RU2480201 (**2013**)	Iron oxide, magnetite, maghemite or $M(II)Fe_2O_4$, wherein M represents Zn, Cu, Co, Ni, Cd, Ba or Mn	1-100nm	Nanoparticles have a coating which contains polycondensated aminosilanes	Hyperthermia, chemotherapy, radiotherapy
RU2481125 (**2013**)	$M^{II}M_2^{III}O_4$, where M^{II}=Fe, Co, Ni, Zn, Mn; M^{III}=Fe, Cr, or maghemite	4-200nm	Nanoparticles functionalized by bifunctional compounds; the structure may also include a polymer and a pharmacologically active molecule	Hyperthermia, MRI
RU2490027 (**2013**)	Ferric oxides or pure iron	1-100nm	At least one therapeutically active substance is bound to the particle	Hyperthermia, chemotherapy, radiotherapy

Table (1) contd….

Cited Document	Material/Particles	Size	Modifications	Possible Use
RU2500622 (**2013**)	Iron oxide	1-100nm	Silicon-containing casing	Hyperthermia, chemotherapy
RU2533487 (**2014**)	Maghemite	< 10nm	Protective coating comprising an adsorbed growth regulating agent for nanoparticles	Biomedical applications, hyperthermia, drug delivery, MRI
RU2558882 (**2015**)	Magnetite	1-100nm	-	Hyperthermia, MRI
RU2567620 (**2015**)	Ferromagnetic metal	1-200nm	Particles are at least partly encapsulated in graphite carbon	Hyperthermia, drug delivery, MRI
US7282479 (**2007**)	Ferrite, magnetite, permalloy	< 1μm	Particles may have an antibody bound to the surface for selective binding to tumor cells	Hyperthermia
US7842281 (**2010**)	$Mn_{0.5}Zn_{0.5}Fe_2O_4$	10-400nm	A composition includes a polymeric material, a drug or radiosensitizing agent	Hyperthermia
US8586095 (**2013**)	Iron oxide	10-300nm	Magnetic nanoparticles are encapsulated in a thermosensitive polymer nanostructure to carry a drug	Hyperthermia, drug delivery, MRI
US9005582 (**2015**)	MnGdFe, ZnGdFe, FeGdB, FeNdB, MnZnGdFe	5nm - 1μm	A biocompatible thermosensitive coating	Hyperthermia, drug delivery
US20140219926 (**2014**)	Iron oxide	20-100nm	Starch coating; polysaccharide-based carrier matrix	Hyperthermia, MRI
US20150165070 (**2015**)	Fe_3O_4, γ-Fe_2O_3, iron mixed oxides with Mo, Cr, Mn, Co, Cu, Ni, Zn	10-80nm	Nanoparticles and aggregates coated with polysaccharide, carboxylic acid, etc.	Hyperthermia, cell tracking, MRI
WO2006102307 (**2006**)	Fe_3O_4, Fe_2O_3, alloys of iron/nickel and alloys of nickel/copper	5-250nm	The particle includes a magnetic core, a metal nanolayer surrounding the magnetic core and a surfactant layer surrounding the metal nanolayer; the metal nanolayer is bound to a biomolecule affine to target cells	Hyperthermia
WO2007142674 (**2007**)	$CoFe_2O_4$, Fe_3O_4, Fe_2O_3	1-800nm	Nanoparticles with a targeting moiety	Hyperthermia, drug delivery

The publication [14] relates to a method of producing organic substrate particles bonded to switchable ferromagnetic nanoparticles with mean diameter 10-1000nm. The switchable ferromagnetic nanoparticle comprises Mn and Fe and/or As and has Fe_2P-structure or Na-Zn-13-structure, or may comprise La, Fe and Si. The described invention demonstrates how to prevent the agglomeration of particles and increase their size. These switchable ferromagnetic nanoparticles are magnetocaloric and showed improved heating properties due to an additional contribution of magnetocaloric effect.

A polyol-type process for obtaining magnetite MNPs for hyperthermal treatment and/or diagnostics of tumors by MRT is aimed at the obtaining MNPs of uniform size with increased SAR value [15].

Nanoparticles comprising 3-100 entities of at least one ferromagnetic metal and graphite carbon wherein such metal particles are partially encapsulated in graphite carbon, are described in [16]. Ferromagnetic particles also include nickel, cobalt, precious metals and their combinations. The ferromagnetic metal particles are uniformly distributed and do not form clusters.

Improved MNP compositions [17] provide an inherent temperature regulator for use in magnetic heating. These compositions have the Curie temperature 40-46ºC and include a polymeric material and optionally a chemotherapeutic or radiosensitizing agent. The described compositions reduce or eliminate the problem of uneven heating, and possess a property to self-regulate the maximum temperature.

Magnetic oxide-quantum dot nanocomposites, methods of synthesis and application of fluorescent MNP-quantum

dot nanocomposites are described in [18]. The magnetic oxide-quantum dot nanocomposite is a magnetic oxide nanoparticle (usually Fe_3O_4) coated with a silica (SiO_2) shell and terminated with thiol group (-SH), and CdSe/ZnS quantum dot linked to a SiO_2-coated magnetic oxide nanoparticle via the thiol group. The formation of a passive coating of inert materials such as silica on MNP surfaces helps prevent their aggregation in blood vessels and improve chemical stability.

A novel heat-generating composition [19] includes a hetero-structure nanomaterial which consists of (a) a metal or a metal chalcogen, a metal pnicogen, an alloy and their multicomponent hybrid structure; and (b) a material comprising at least one component selected from the group consisting of metal, metal chalcogen, metal pnicogen, alloy and the multicomponent hybrid structure thereof; where the first material is enclosed in the second material. Either the first or second material is magnetic. The specific loss power of such a composition is much higher than that of conventional nanomaterials and may be controlled by changing the ratio of materials.

A biodegradable iron oxide nanoparticle gel for hyperthermia includes a polysaccharide-based carrier matrix and starch-coated iron oxide [20]. The gel adheres to tissue and has sufficient deformability to fit into the tumor site. Due to its mechanical properties the gel remains in place during treatment. The gel releases iron oxide nanoparticles for uptake by tumor cells.

Magnetic particle dispersions comprising coated single-crystalline and/or polycrystalline single nanoparticles of iron oxides and particle aggregates (multicore particles) with improved non-linear magnetization behavior and heating properties in alternating magnetic fields are described in [21]. When measured in a magnetic particle spectrometer the particle dispersions show a pronounced overtone structure, especially in the higher harmonics, which surpasses all previously known particle systems. Therefore, the dispersions are especially useful for applications such as magnetic particle imaging. In addition, new particle dispersions are suitable for treatment of iron deficiency anemia, passive partial body hyperthermia, and MRI.

An improved method for preparing ferrite superparamagnetic nanoparticles engineered by magnesium doping, and a technique for applying it to hyperthermia are provided in [9] (Fig. (**2**)). Mg-based ferrite nanoparticles are known to exhibit excellent biocompatibility and high temperature self-heating characteristics but are difficult for synthesis. The method includes mixing a raw material comprising Fe (III) acetylacetonate, magnesium and a solvent; performing primary heat treatment to create nuclei of nanoparticles; and secondary heat treatment to grow the nuclei to form nanoparticles, followed by washing, centrifugal separation, drying, and grinding of nanoparticles. The processed superparamagnetic Mg-doped ferrite nanoparticles are, for example, $MgFe_2O_4$, $MgZnFe_2O_4$, or $MgMnFe_2O_4$. The obtained Mg-based ferrite nanoparticles are claimed useful for treatment of brain tumors and non-malignant intracranial disorders.

A ferric oxide magnetic powder with high hysteresis heat generating capability and its preparation are described in [22]. Predominant constituents are ferriferous oxide or ferric oxide, or ferriferous oxide and ferric oxide; the iron and oxygen content are 69.0-72.4% and 27.6-31.0%, respectively.

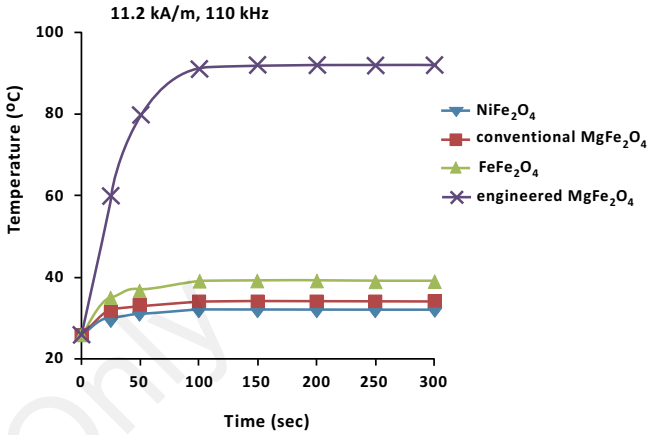

Fig. (2). Comparison of heat generation temperature by different MNPs [9].

A method for preparing a double-layer modified nanometer ferroferric oxide magnetic fluid disclosed in [23] is simple and convenient. The product has strong controllability and superparamagnetism and can be used in MH, magnetic separation, targeted drug therapy and bioengineering materials.

The publication [24] relates to a novel high performance vortex magnetic-domain iron-based nanomagnetic hyperthermia medium. The medium represents a core with vortex magnetic-domain iron-based nanoparticles coated with a biocompatible organic polymer or an inorganic material to form a magnetic sol. The nanomagnetic hyperthermia medium has a vortex magnetic state, high magnetic saturation intensity, good dispersion stability, high hysteresis heat loss, high heat production efficiency (SAR). Moreover, it is safe and non-toxic.

The use of protein-coated, iron-based MNPs as a MH medium is described in [25]. The surface of the MNP core is coated with protein to form stable magnetic hydrosol. The MH medium has good biocompatibility, stable magnetic soil and high performance.

The invention [26] addresses an important problem in thermotherapy, that is, the heating value of a medium and precise control of temperature. Indeed, an insufficient tumor heating can lead to failure of therapy whereas an excessive heating of normal tissue can cause burn injury. The heating value of the iron oxide MNPs in the high frequency magnetic field (30kHz-1MHz) can be controlled by setting the particle size and specific surface area: the mean particle diameter is within the range of 5-35 nm, and the specific surface area 35-150m^2/g.

An improved method [27] for producing an aqueous dispersion comprising Fe-containing ferromagnetic particles includes: (i) mixing an aqueous solution containing iron ions and an aqueous alkali solution and precipitating an iron containing hydroxide in the resulting mixture; (ii) subjecting the mixed aqueous solution to a hydrothermal treatment to form

ferromagnetic particles from the hydroxide; and (iii) washing ferromagnetic particles; the latter are kept wet in the step (iii) or after that step. The aqueous dispersion of MNPs is anticipated to be suitable for MH.

The publication [28] relates to N-Zn based ferrite MNPs having a core comprising $Ni_{(1-i)}Zn_iFe_2O_4$ ($0.2 \leq i \leq 0.6$) and a shell of an amorphous SiO_2 for covering the core. Average particle size is 10-20nm. These MNPs provide temperature rise of 4-15ºC at the application of 210 Oe magnetic field with frequency of 15kHz.

A major aim of the invention [29] is the development of a magnetic material with a high biocompatibility and an adequate susceptibility to magnetic fields. These materials are constituted by a biocompatible vitreous matrix in which a magnetic crystalline phase is dispersed. The magnetic crystalline phase can be magnetite. The invented materials may be obtained with three methodologies: co-precipitation, melting, and sintering. Due to its biocompatibility the obtained material can be used for thermal treatment of neoplasms.

The improvement of MNPs reported in [30] allows their selective heating at a magnetic field frequency due to a specific size and/or composition. The nanoparticles include $CoFe_2O_4$, Fe_3O_4, Fe_2O_3 or their combinations and may comprise at least one targeting moiety, e.g., an antibody, ligand, receptor, cross-linking agent or nucleic acid. The invention also relates to the use of such nanoparticles for remote alteration of protein structure via activation or inhibition of thermosensitive gene promoters and drug delivery.

Polymer-coated iron oxide magnetic nanoparticles [31] are suitable for application in magnetic particle imaging, magnetic sentinel lymph node biopsy, and fluid MH. The nanoparticles are coated with a copolymer of poly (maleic anhydride alt-H_2C-CH-R1)-polyethylene glycol (PMAR-PEG), wherein R1 is a hydrophobic moiety. The molecular weights of the PMAR and PEG portions of the copolymer and the core diameter of the nanoparticles are selected in order to produce optimal performance for specific applications. The nanoparticles provide previously unachieved levels of stability (e.g., via reduced agglomeration) and customizability (e.g., tuned blood circulation half-life).

An increasing number of studies analyze magnetic particles, nanoparticles, materials or compositions as drug carriers or drug delivery systems for MH. The particles can be administered intravenously or intratumorally and can be heated by an electromagnetic field, where the particles are combined with or attached to drugs or cancer cell recognizing antibodies. Recent improvements of such delivery systems are aimed at the increase of biocompatibility and treatment efficiency and the reduction of severe adverse effects. Some of them are discussed below.

A carrier for drugs and biologically active substances for diagnosis and treatment is described in [32]. The carrier is a material sensitive to external magnetic or electric fields and consisting of magnetic or ferroelectric material coated with a film of biocompatible, thermosensitive, biodegradable polymer and/or distributed in the temperature sensitive environment. Magnetic or ferroelectric materials consist of substances with a large value of magnetocaloric or electrocaloric effect (1-13K), have the temperature of magnetic or ferroelectric phase transition 33-37ºC and are selected from lanthanide, transition and precious metals, their alloys and compounds. The carrier enables the controlled drug delivery and release in the disease site.

The patent [33] relates to stable complexes for MRI as well as for drug delivery systems with controlled release by heating. Stable complexes consist of metal oxides - iron, cobalt, or their alloys - in the form of nanoparticles and bifunctional compounds, the latter selected from thiols, carboxylic acids, hydroxamic acids or their phosphoric esters or salts, having an aliphatic chain containing a second functional group in the terminal position. The method of producing the complexes involves reaction of dispersion of nanoparticles in an organic solvent with a suitable binder; the mixture is stirred for several hours at low temperature and the obtained product is then cooled and separated by centrifuging, and then can be cleaned via repeated dispersion in a suitable solvent and repeated deposition.

A magnetic system suitable for drug delivery via hyperthermia is described in [34]. The structure of the magnetic system contains MNPs of general formula $M^{II}M_2{}^{III}O_4$, where M^{II}=Fe, Co, Ni, Zn, Mn; M^{III}=Fe, Cr, or maghemite which are functionalized by bifunctional compounds R_1-$(CH_2)_n$-R_2 (where n = 2-20, R_1 is selected from CONHOH, CONHOR, $PO(OH)_2$, PO(OH)(OR), COOH, COOR, SH, SR; R_2 is an external group selected from OH, NH_2, COOH, COOR; R is an alkyl group or an alkaline metal selected from C_{1-6}-alkyl and K, Na or Li, respectively).The structure also includes a polymer carrying a pharmacologically active molecule. The inventors characterized their magnetic system as biocompatible and stable.

A magnetic medical powder [35] can be used as a carrier for drug delivery, an immunolatex, immunobeads, a medium for hyperthermia, etc. The powder comprises a particle of a ferromagnetic material and a biologically inert coating layer on its surface. The coating layer includes an alkoxide compound hydrolysate. The powder is claimed to be a safe material with perspective performance.

The technical solution [36] provides nanomaterials for use in MH in conjunction with targeted drug delivery. MNPs are encapsulated in a thermosensitive polymer nanostructure having a lower critical solution temperature of 40-45ºC. The thermosensitive polymer nanostructure may carry a drug. When MNPs are heated to 40-45ºC with an alternating magnetic field the thermosensitive polymer nanostructure collapses to release the drug, thereby allowing for a concurrent heat-and-drug treatment.

A system that enables the delivery of therapeutic agents to the tumor site and drug release upon heating is described in [37]. The delivered agents may be chemotherapeutics, radiosensitizers and other appropriate compounds. MNPs encapsulated by therapeutic agents in a biocompatible coating are supposed to be delivered to the tumor by attenuated bacteria that reside at tumor sites. An alternating magnetic field device with a prescribed frequency can be used to induce heating of MNPs, thereby melting the coat and releasing the drug.

The publication [38] relates to stem cells loaded with bifunctional MNPs (nanoparticle-loaded stem cells (NLSC)) that both: a) heat in an alternating magnetic field, and b)

provide MRI contrast enhancement for MRI-guided hyperthermia. The nanoparticles in NLSC are non-toxic, do not alter stem cell proliferation and differentiation, and are heated in an alternating magnetic field. NLSC can deliver hyperthermia to hypoxic areas in tumors for sensitization to subsequent treatment, thus focusing on the most treatment-resistant parts of the tumor.

MNPs prepared of ferric oxides or pure iron containing an oxide-containing layer, where a therapeutically active substance is bound to MNPs have been analyzed in [39]. The release of the therapeutic agent is dependent on a variable magnetic field. The main advantage of the invention is the reduction of an uncontrolled drug release during nanoparticle delivery to the tumor.

A composition described in [40] reports on MNPs having magnetic properties and forming a single magnetic domain, a biocompatible coating material, and a targeting ligand bound to an uncoated or coated portion of the particle or intercalated into the coating. The composition provides selective delivery of magnetic fields to the diseased tissue in a safe and effective manner, with minimal invasion, and short treatment periods.

The invention [41] relates to a hyperthermia agent which comprises a cytokine or a vector in which the cytokine gene is integrated so that the cytokine can be expressed in tumor cells, and magnetic fine particles. The magnetic particles may comprise ferrite, permalloy or magnetite, and the cytokine can be selected, e.g., from interleukin-2 or granulocyte macrophage colony stimulating factor. During hyperthermia the cytokine is stimulated by immunocompetent cells and activated, therefore, the therapeutic effect is markedly improved.

A targeted MNP based composition [42] consists of an effector molecule and a guidance molecule in a weight ratio of 1:0.0001-0.2.The former is a magnetic particle (< 1000nm) and SAR 10-7000W/g Fe. The guidance molecule (also < 1000nm) can be an antibody, a ligand or a magnetic particle. The targeted MNP-drug is prepared by coupling a magnetic particle and a guidance molecule in water, organic or inorganic substance. The resulting composition is suggested to be applicable in targeted MH treatment/tumor thermoablation.

An improved iron oxide/gold core-shell nanoparticle delivery system [43] represents a biologically active substance bound to the surface or located inside the gold shell of the nanoparticle. Depending on the size of the core, the particles are single domain magnetic or superparamagnetic. These systems are used for targeted delivery of biologically active substances, MH, imaging or their combinations.

A delivery system that comprises a fine magnetic particle for MH with minimal heating of surrounding tissues used an antibody for selectivity [44]. A high frequency magnetic field having (1kHz-1MHz) is preferable. The monoclonal antibody HB4C5 against lung cancer or 17-1A against colon cancer antigens were used. In similar approach [45] the surface of MNPs (average size 1-100nm) is coated with a compound having aggregation-inhibitory effect, and a tumor cell targeting antibody is bound to the compound. These MNPs enable thermotherapy to be conducted selectively to the tumor without affecting normal cells.

An improved method for cancer detection and treatment is provided in [46]. In particular, it describes a particle for introduction into a system for enhancing optical contrast between tumor cells and surrounding tissue, and for inducing tumor cell death while minimizing damage to non-malignant counterparts. The particle includes a magnetic core, a metal nanolayer surrounding the magnetic core and a surfactant layer around the metal nanolayer. A biomolecule affine to target cells is bound to the metal nanolayer. The particle exposed to an electromagnetic field induces hyperthermia in the target cells whereas damage to normal tissues is reduced.

MNPs suitable for MRI and MH are provided in [47]. The metal particles are magnetically active and are much smaller than 100nm. The magnetic particles are functionalized with organic biocompatible ligands that permit transport of nanoparticles to the disease site.

A heat-dissipating composition for therapeutic hyperthermia [48] is presented by a sensitization material selected from the group consisting of MNPs and drugs or radioisotope. The composition may have heat dissipating effects and therefore be synergistic on tumor cell death.

In some cases, MNPs can be administered simultaneously with anticancer drugs [49]. The drug free nanoparticles are coated with polycondensated aminosilanes. Simultaneous presence of the nanoparticles and the drug in the body is directed at synergy of the two modalities. According to the invention the nanoparticles consist of iron oxide, magnetite, maghemite or M (II)Fe_2O_4, where M is Zn, Cu, Co, Ni, Cd, Ba or Mn. The diameter of nanoparticles is 10-20nm. The combinations presume MH, thermotherapy with magnetic fluids, radiation therapy and chemotherapy.

In regard to improving selectivity, liposomes and other lipid structures have been widely proposed for targeting drugs to specific locations [50]. A number of attempts have been made to develop a wave-absorbing magnetic particle core liposome compositions which substantially improve selectivity and allow the particles to pass through physiological barriers. Exposure to electromagnetic radiation caused selective heating and destroyed the target cells. As demonstrated in [51], thermosensitive liposomes with encapsulated nanoparticles can be used as therapeutic or diagnostic tools. Heating of thermosensitive liposomes at $\geq$Tm results in local release of nanoparticles and their interaction with target cells.

An electromagnetic wave-absorbing surface modified magnetic particle described in [50] is coated with an amphipathic organic compound and an amphipathic vesicle forming a controlled size particle core liposome which can pass through physiological membranes. Cells absorb coated particles, and the inductive heating of magnetic particles increases intracellular temperature and selectively kills target cells.

A magnetic vesicular composition for MH [52] comprises the material obtained by forming a lipid molecular layer with a functional molecule to positively charge the vesicular material. The vesicular material approaches target cells, and when an AC magnetic field is applied heat is generated by magnetic hysteresis loss effect to kill target cells.

Table 2. Methods of MH Induction.

Cited Document	Magnetic Material/Particles Type	Field Parameters	Heat Temperature	Advantages
EA019412 (**2014**)	Ferromagnetic particles, 50-100nm	Alternating magnetic field (f ≥ 10kHz)	43-44ºC	Thermal destruction of tumors not affecting healthy tissue
RU2026083 (**1995**)	Ultrafine iron particles, 0.2-1.0μm	HF	> 43ºC	Uniform heating of tumor tissue; reduction of MH toxic effects
RU2034548 (**1995**)	Ferromagnetic particles in the biologically active liquid (aloe extract), > 4μm	HF	41.5ºC	The increased tumor destruction; the decreased electromagnetic radiation dose
RU2082458 (**1997**)	Ferromagnetic particles, 2-30μm	HF, SHF	42-45ºC	Improved accuracy and uniformity of the intratumoral temperature
RU2203111 (**2003**)	Magnetically controlled preparation (γ-Fe_2O_3)	Constant magnetic field (0.2-4 T), alternating magnetic field (50-1000kHz)	42-45ºC	Partial and complete tumor regression in experimental animals; reduction of MH toxic side effects
RU2291677 (**2007**)	Magnetically controlled preparation (γ-Fe_2O_3)	Constant magnetic field (0.2-4 T), alternating magnetic field (50-1000kHz)	42-45ºC	Reduction of solid tumor volume without toxic effects
RU2295933 (**2007**)	Particles consist of a substance with a large value of magnetocaloric effect, e.g., the alloy $Fe_{0.49}Rh_{0.51}$, 1 nm-8μm	Constant or alternating magnetic field	40-42ºC	Uniform heating of tumor mass without effecting healthy tissue
RU2468447 (**2012**)	Colloidal solution of silver nanoparticles	SHF (915MHz)	42ºC	Increased cytotoxicity of nanoparticles
RU2506971 (**2014**)	Iron nanoparticles	UHF(12.7MHz)	42-43ºC	The enhancement of the anti-tumor thermo-chemotherapy effect without toxicity effects increasing
US4983159 (**1991**)	Ferromagnetic particles, 5-50μm	Alternating magnetic field (25-50kHz)	≥ 42ºC	Hysteresis heating of the particles; necrosis of the neoplasm
US7951061 (**2011**)	Iron, powdered iron, magnetic alloys, magnetic fluids	Alternating magnetic field (1kHz - 1GHz)	43ºC	Selective delivery of alternating magnetic field with known and controllable amplitude to a specific area of the body
US8709488 (**2014**)	Magnetic, diamagnetic, ferromagnetic, paramagnetic nanoparticles; gold, diamond, platinum, and/or carbon nanoparticles	Electromagnetic radiation, ultrasound, or alternating magnetic field	35-43ºC (drug release); 43-50ºC (thermotherapy)	The possibility of combination with chemotherapy; selective targeting of tumor tissue

MH IMPLEMENTATION: USE AND APPROACHES TO DEVELOP METHODOLOGIES

Several techniques are available for inducing MH regionally or locally or over the body. Some of these techniques are summarized in Table **2** and discussed below.

Regional MH implemented as described in [53] comprises the exposure of the body area to electromagnetic radiation until the rectal temperature reaches 42.2-42.5ºC. The temperature is to be supported within given time interval by supplying electromagnetic oscillation power from emitters, providing minimum radiation power in vertebral column projection and on the skin. An area from the shoulder to the lower half of the thigh is irradiated with an incident power equal to ≤ 400W, and the body temperature is maintained at 42.2-42.5ºC for up to 180 min. This method provides the enhanced effectiveness of treatment and reduced risk of complications.

A significant number of recent studies deal with local MH due to development of new optimized materials/particles. Known methods of local MH are based on two approaches. The first one relates to the use of ferromagnetic or metal particles within the tumor mass or in its close proximity followed by exposure to a magnetic or electromagnetic field (HF, UHF, SHF, constant magnetic field, etc.) [2, 54-66]. The second approach is represented by methods of in-

troducing particles into the tumor where the particles are combined with or attached to anticancer drugs or cancer cell directed ligands [67-71].

Administration of ferromagnetic materials into the tumor with subsequent exposure to HF field, where the materials are ultrafine iron particles of 0.2-1.0μm, is described in [54]. The method provides uniform heating and destruction of the tumor tissue, and allows for reducing side effects of MH.

Use of a suspension of ferromagnetic particles in the biologically active liquid (such as aloe extract) administered to the tumor area and exposure to HF electromagnetic field (temperature 41.5ºC) led to and increased tumor destruction whereas the surrounding tissue was spared, and the electromagnetic radiation dose decreased [55].

The technical effect of the method [56] is an improved accuracy and uniformity of intratumoral temperature. The intratumorally injected ferromagnetic particles with Curie temperature 42-45ºC and subsequent heating with electromagnetic field (SHF or HF) maintained the set temperature in the heated tumor zone.

The publication [57] describes a method for selective destruction of tumor cells with ferromagnetic particles within the tumor and a local heating to 42-45ºC. The time of heating depends on tumor characteristics, size, localization and type of ferromagnetic particles selected for induction heating of a particular tumor. The heat is applied when the tissue blood content is reduced, i.e., at the moments of patient's exhalation and heart diastole. Heating is carried out in an automatic mode. The range of temperature is controlled by means of microwave frequency deep-seated thermometer. Laser radiation is applied in addition to the heat to increase the damage to tumor cells at the moments of the power supply deficiency due to blood circulation rhythms. The proposed method of ferromagnetic particle induced heating in the phases of reduced tissue blood supply provides an increased efficacy of heating as well as the reduced heat dissipation. Consequently, the effectiveness of treatment is increased.

The method of inductive hyperthermia [58] implies a regional introduction of a magnetically controlled preparation (e.g., γ-Fe_2O_3) to the tumor with its subsequent concentration, fixation in a static electromagnetic field and heating in an alternating electromagnetic field through a water layer having a constant temperature. The method provides tumor regression in experimental animals and allows for reducing side effects of MH.

The method [59] relates to a hyperthermal treatment of primary and metastatic tumors using a high frequency electromagnetic field or a high density infrared light followed by local or whole body temperature increase up to 43.5ºC. Prior to heating the tumor is infiltrated with an aqueous silver solution (20-50mg/l) and exposed to 200-1000 Oe magnetic field. The method increases the efficiency of treatment due to low toxicity and potent cytotoxicity of silver ions.

A combination of metal nanoparticles and microwave radiation hyperthermia in which tumor cells are exposed to silver nanoparticle colloidal solution (34μg/ml) along with microwave irradiation (915MHz) for 30 min yielded synergy of the two modalities compared to each individual impact [60].

The invention [61] describes a method for local MH based on absorption of alternating magnetic field energy by magnetic particles possessing high coercive fields introduced into the tumor. The method can be used for thermal destruction of tumors with little to null damage to normal tissues. In particular, the invention solves the problem of MH efficiency by controlling the field amplitude taking into consideration the change of intratumoral temperature, optimization of the particle size and coercive force, and the alternating magnetic field parameters such as the frequency and range of amplitude regulation.

A non-invasive method of treatment [62] offers a localized magnetically coupled, radio-frequency (RF) induced hyperthermia mediated by a material which is non-toxic, biocompatible and has incorporated iron-containing crystals of such size, amount, composition, and magnetic properties to impart a coercive force of at least 200 Oe to the material. The RF magnetic field has a frequency within 10kHz.

A necrotic death of the heated tumor in which particles capable of exhibiting hysteresis heating are injected in the tumor proximity and subjected to an alternating magnetic field is described in [63]. The frequency of the field is low to minimize eddy current and dielectric heating. The particles are initially embedded within a biologically inert liquid carrier which facilitates their insertion and which becomes non-liquid in the body to hold the particles in place. The carrier may contain an opaque material to enhance its visualization in radiographic examination. The authors provide a procedure which can be utilized with a wide variety of tumor types and localizations without significantly endangering non-malignant tissues.

Similar process is reported in [64]. The document relates to a necrosis of neoplasms using hyperthermia by particles capable of exhibiting hysteresis heating when subjected to an alternating magnetic field. The particles are of a size of $\geq$2 microns, so they are unlikely to be absorbed by tumor or surrounding cells. Alternating magnetic field is of a frequency greater than that sufficient to cause a neuromuscular response, and is less than that causing an eddy current heating and/or dielectric heating of normal tissues. The neoplasm is maintained within the field for a time sufficient to heat the particles and the neoplasm to at least 42ºC to cause tumor necrosis.

The invention [2] relates to a method for local tumor treatment comprising the steps of: (i) selecting a magnetic material which has a magnetic heating efficiency of at least about $4.5x10^{-8}$ J. m./A.g, when magnetic field conditions are $\leq 7.5x10^7$A/s; (ii) delivering the magnetic material to the tumor site; and (iii) exposing the magnetic material in the patient to a linear alternating magnetic field with a frequency of $\geq$ 10kHz and a field strength such that the product of field strength, frequency and the radius of the exposed region is < $7.5x10^7$A/s to generate hysteresis heat in the tumor. The ferromagnetic material can be selected from iron, manganese, arsenic, bismuth or their combinations. The provided method seeks to ameliorate the problems associated with penetration depth and inadequate heat localization.

An efficient MH approach [65] is based on the so called magnetocaloric effect where the particles introduced into the tumor serve for generating heat upon the application of electromagnetic field. The particles consist of a substance with a large value of magnetocaloric effect, having the temperature of magnetic phase transition close to that of the human body and are selected from the group comprising rare-earth, transition and precious metals as well as their alloys and intermetallic compounds (e.g., iron-rhodium alloy particles such as $Fe_{0.49}Rh_{0.51}$).

A novel method of treatment [66] implies the intravenous administration of a pharmaceutical composition comprised of functionalized magnetic gold nanoparticles coated with a polymer giving them a positive charge (PEG, dextran sulfate or polyethylenimine), and a pharmaceutically acceptable carrier, followed by the exposure of the tumor to an intense and rapidly fluctuating magnetic field (1-30MHz) sufficient to induce eddy currents capable of hyperthermally ablating cancer cells.

A method [67] allows for reducing a solid tumor volume without toxic effects. The method for treating solid tumors by inductive hyperthermia comprises regional introduction of a magnetically controlled preparation to the tumor area with its subsequent concentration, fixation in a static electromagnetic field and heating in an alternating electromagnetic field, wherein a magnetically controlled preparation is mixed with the chemotherapeutic drug alkeran.

The rationale of the method [68] is the enhancement of the antitumor thermochemotherapeutic efficacy with minimal undesired toxicity. The approach presumes a combined effect of metal nanoparticles and MH, that is, a suspension of iron nanoparticles (1.25mg/kg) is administered intratumorally, then methotrexate (0.2mg/kg) is administered peritumorally and the tumor is subjected to localized heating (42-43ºC) with the electromagnetic emitter of UHF-range (12.7MHz) for 10 min.

Administration of a thermotherapeutic magnetic composition and application of an alternating magnetic field to inductively heat the thermotherapeutic magnetic composition, is described in [69]. The magnetic material composition comprises a magnetic particle attached to a cell recognizing ligand. The method provides safe and efficient treatment. A similar method [70] is based on administering of an antibody-coated and/or drug-containing nanoparticle composition and subsequent temperature increase.

A heat therapy kit that comprises a pharmaceutical agent containing a T-cell recognizing antibody and magnetic fine particles is aimed at achieving tumor regression by enhancing systemic antitumor immunity [71].

A series of new MH methods use implants, applicators, etc. The publication [72] describes local heating of tissues in an alternating magnetic field of high frequency, where an applicator of polymeric material modified with electrically conductive ferromagnetic particles is placed inside the heated object. The method provides precisely localized and controlled hyperthermia.

The application of a solid medical product (heated by an alternating magnetic field) for MH after surgical tumor ablation is described in [73]. The product represents a surgical implant in the form of a biocompatible fabric, sponge or film and contains magnetic particles that generate heat under an alternating magnetic field. The invention ensures a considerable efficacy compared with chemotherapy alone.

A method for personalized intrasurgical local hyperthermia [74] implies the use of an individual applicator with a ferromagnetic filler, in particular, ferromagnetic ferrite particles with Curie temperature ~45ºC. The technical result of the method is the exclusion of direct contact of the ferromagnetic filler with the operated tissue, enhanced dissolution of active substances and reduction of recurrence of disease.

A method for reducing the tumor mass utilizes localized, magnetically-coupled, RF-induced hyperthermia [75]. The method involves the implanting of a material in and/or closely adjacent to the tumor area. The material is non-toxic and has encapsulated ferromagnetic particles of the size, amount, composition, and ferromagnetism to develop a heating value of up to 1W/g through essentially only hysteresis heating, under an applied field of 20-200 Oe at a frequency 10-600kHz, or under an applied field of ~2000 Oe and a frequency < 40Hz. Such heating value is sufficient to kill tumor cells whereas muscle and nerve responses are minimized.

MH can be combined with radiation therapy and/or chemotherapy. The document [76] provides systemically introduced nanoparticles to create focused local hyperthermia expected to enhance the effect of ionizing radiation. Advantages include an increased perfusion or reduced hypoxia in the treatment area.

An increasing number of publications deal with simultaneous use of MH and other imaging and detection systems. In particular, [77] describes a system and method for performing and monitoring MH with targeted MNPs. The system comprises a low field MRI unit and a RF unit configured to register MRI data from the target area. A hyperthermia system is coupled to the low field MRI unit and is capable to generate a hyperthermia excitation field configured to cause MNPs rotation with a lag which results in warming of the target zone. The MRI unit acquires imaging data from the target area and reconstructs them to determine spatial distribution of MNPs and temperature.

A method for simultaneous magnetic induction heating, imaging and temperature detection in tumor cells is provided in [78]. The method comprises the combination of MNPs with magnetic induction heating, fluorescent quantum dot imaging and measurement of temperature.

Approaches to MH implementation also include the use of computerized tools for assistance in treatment planning. A computer aided simulation and suitably configured equipment for comprehensive overview of therapeutic opportunities are provided in [79]. The hyperthermic treatment comprises the application of a magnetic field within the tumor by means of a magnetic field applicator. In at least one depot volume, thermal energy can be introduced by MNPs, paramagnetic and/or superparamagnetic nanoparticles deposited in the body. The planning of thermotherapy is possible due

to field strength values and calculated temperature distributions.

Examples of tumor regression and/or ablation by MH have been achieved in cervical cancer, tumors of parenchymatous organs, laryngeal and laryngopharyngeal cancer, and glioblastoma. The invention [80] relates to a method for treating patients with disseminated cervical cancer. The suggested method provides local HF hyperthermia in the cervical canal at 42.5-43ºC with electromagnetic field frequency of 13.56MHz right before γ-irradiation. The method provides partial or complete tumor regression.

Cancer of parenchymatous organs can be approached via catheterization of the tumor supplying vessel and administration of a ferrosilicon composition and, optionally, ivalone via catheter [81]. In 3-4 weeks after organ occlusion local electromagnetic high frequency hyperthermia is conducted at 44-46ºC in the tumor for 45-60 min. The method provides an improved rate of remission in patients with late stages of the disease.

Laryngeal and laryngopharyngeal cancers are treated by combinations of surgical and radiological methods [82]. After the tumor is excised an intraoperative individual tissue equivalent applicator consisting of a self-polymerizing material with conductive ferromagnetic particles is used. Local MH is performed through the applicator (42-43ºC for 60 min). By days 7-8 post surgery the applicator is removed; 8-12 days later the area of the extracted tumor is irradiated again. The method decreases the frequency of complications in healthy tissues and allows to reduce the dose of radiation.

A method for treatment of glioblastoma [83] presumes incorporation of biocompatible MNPs into the brain and subjecting the patient to an external static magnetic field to provide movement of migrating cancer cells in the external magnetic field (magnetotaxis). Then the cells undergo surgical removal or MH.

DEVICES FOR MH

Two groups of devices are currently used in anticancer MH. The first group implies direct irradiation of the diseased tissue with an electromagnetic field. This approach is also known as interstitial hyperthermia (see, e.g., [84]). To some extent it is invasive and rather aggressive towards the patient since, for maximum control of the irradiated area, antennas have to be implanted into the tissue by surgical methods, e.g., with a catheter or by insertion of an active radiofrequency electrode into the tumor for the release of electromagnetic field energy [84].

Currently used invasive methods and devices have several limitations in regard to heating of deep areas of the tumor. For example, in the case of the interstitial antenna, the depth of insertion is not an arbitrary parameter. It depends upon the length of the antenna which in its turn is determined by the wavelength value [85]. In the case of RF electrodes, the current paths are dictated by the locations of the source and the sink electrodes and often require several electrodes to conform to the approximate contour of the desired heating volume. The use of multiple electrodes increases the risk of bleeding and tumor re-implantation [85].

Improvements are aimed at rapid and uniform heating of tumors, reducing the risk of healthy tissue thermal damage (summarized in Table **3**).

A device for treating neoplasms [86] consists of a power source, a high frequency generator, emitters, a temperature measuring and control unit with heat sensors and a high frequency power distribution unit. Each emitter is formed as a group of needle electrodes. A high frequency power distribution unit comprises the coils connected with electrodes. The device provides fast and uniform tumor heating to the required temperature.

The device for local MH [87] allows reducing the risk of healthy tissue thermal damage. It consists of a UHF-field generator and at least two electrodes with an applicator containing a liquid dielectric, a tool for electrode orientation and liquid dielectric supply, a system for UHF-field generator control, needle-like sensors with eight-channel thermometric device, a system for displaying and recording information. The temperature is controlled within the range of 42-45ºC.

A device designed to increase MH selectivity includes a RF source, an amplifier, a sensor, a feedback amplifier and a modulation signal generator [88]. The RF source produces a signal which is modulated by the generator, amplified and directed to the target. The sensor receives a feedback signal from the target that is directed to the feedback amplifier, wherein the feedback signal is amplified by the feedback amplifier and modulates the source signal to generate a target modified signal.

An improved MH device [89] consists of an electromagnetic energy transmission facility for targeting the energy, comprising a conductive metallic electrode material as a coating or mesh wire. A flexible carrier coated with the conductive metallic electrode material is porous, making possible transport of water (sweat). This material is not isolated from the skin; it is opposite to at least one counter electrode or one oppositely charged capacitor electrode. Either the coated flexible carrier or mesh wire consists of the number of positive and negative sections or electrodes. The electromagnetic energy transmission facility is attached to a RF source providing radio frequencies 10kHz-50 MHz. The device allows applying AC or RF, high current low electric field for deep heating. Besides, the electrode geometry and arrangement are optimized to achieve optimal temperature, SAR and electric field distribution.

An apparatus for RF thermotherapy treatment [90] comprises a hollow toroidal applicator which resonates at a specific RF and generates a high density of uninterrupted magnetic flux within the hollow. A rotatable antenna is connected to a source of RF power mounted inside the applicator to couple with the electromagnetic field of the applicator. The organ to be treated is interposed through side apertures or through the space created by removing a segment of the toroid which has orifices of predetermined cross sectional areas through which a tubular zone of high magnetic flux travels through the tumor and normal tissue. More heat is induced in the tumor than in normal tissue.

A device capable of selectively heating a desired body region and in particular, deeply located tumor portions, in-

Table 3. Devices Used in Antitumor Hyperthermia.

Cited Document	Main Blocks	Field, Parameters	Advantages
CN103750902 (**2014**)	Magnetic induction therapy apparatus body, a medical bed	HF	Effective heating of the tumor
JP2006116083 (**2006**)	Static magnetic field application section, an electromagnetic wave irradiation section, temperature measurement section, magnetic flux converging section	Constant magnetic field, HF field	Low invasiveness of thermotherapy
JP2008200296 (**2008**)	A pair of coils and electrodes, a high-frequency power source	HF	Uniform heating distribution
RU2063255 (**1996**)	A power source, a high frequency generator, emitters, a temperature measuring and control unit with heat sensors, a high frequency power distribution unit	HF, f = 13.56MHz	The fast and uniform heating of a malignant neoplasm to the required temperature
RU2211713 (**2003**)	A generator unit, an inductor unit, ventilator, an envelope for controlling temperature, a capsule having fixators, a permanent magnet	Constant magnetic field (up to 4 T), alternating magnetic field	The device can be used in experiment; enhanced efficacy of treatment
RU2372116 (**2009**)	A UHF-field generator, electrodes with an applicator containing a liquid dielectric, a tool for electrode orientation and liquid dielectric supply, a system for UHF-field generator control, needle-like sensors with eight-channel thermometric device, a system for displaying and recording information	UHF, f = 40.68MHz	Reduced risk of healthy tissue thermal damage
RU2482891 (**2013**)	A radiofrequency source, an amplifier, a sensor, a feedback amplifier, a modulation signal generator	HF, f = 13.56MHz	Increased selectivity of hyperthermia
US5099756 (**1992**)	A hollow toroidal applicator, a rotatable antenna, a source of radiofrequency power	RF, f = 100kHz - 1000MHz	Destruction of the tumor without injury to adjacent tissue
US7945335 (**2011**)	Magnetic field source, an energy source	Gradient DC magnetic field, RF field (f = 100-200MHz)	Selective heating of a small portion of a tumor without healthy tissue thermal damage
US8463397 (**2013**)	Generator of radio-frequency electromagnetic fields, an amplifier, a transmitter, a direct temperature measurement system	VLF-SHF	Device is suitable for use with nanoparticles;direct control of temperature
US8527063 (**2013**)	Conductive button,a magnetic rotor, a temperature sensor	HF, f > 1MHz	Reduced side effects and non-desirable heating

cludes a pair of magnetic poles for applying an alternating magnetic field [91]. These two magnetic poles are laterally arranged on the surface of the body and have time varying polarities opposite to each other, generating a line of magnetic force including a component perpendicular to the body surface in the vicinity of the magnetic poles.

Novel thermotherapeutic apparatus [92] is aimed at forming a substantially uniform heating distribution in the body using high frequency. The apparatus comprises a pair of coils for the formation of a high frequency magnetic field, a pair of electrodes for a high-frequency electric field, and a high frequency power source. It employs the induction heating coils and induction heating screen-like or dendritic electrodes for preventing a high frequency eddy current. The device is capable of executing dielectric heating and induction heating simultaneously or alternately at certain time difference.

Alternatively to these invasive techniques the second group of MH devices is based on the use of magnetic particles, nanoparticles or materials as a medium for dissipating

heat in living tissues. The application of non-invasive devices does not involve surgical implantation of antennas or electrodes. Rather, used are the magnetic fluids made of biocompatible fine particles or MNPs stabilized to prevent aggregation [84]. Mechanisms of energy dissipation in the form of heat are largely related to losses due to hysteresis and to relaxation and friction [84]. The use of non-invasive devices helps overcome technical restrictions of existing invasive hyperthermia approaches, e.g., in respect to the controlled and precise local heating or targeted drug release. In another aspect, the progress in this field requires development of devices capable of focusing heat into tumors without damage to adjacent structures thus avoiding a major disadvantage of current systems [85]. Table **3** presents examples of non-invasive devices.

An alternating magnetic field application device [93] is capable of heating magnetic or magnetized substances in tissues and can be used for MNP based thermotherapy. The device comprises a large applicator having a magnetic yoke and two opposing pole shoes separated by a field gap on the yoke, and two magnetic coils associated with a pole shoe for generating a substantially homogenous alternating magnetic field of certain strength in the field gap. The device provides therapeutically adequate irradiation of relatively small zones.

A device for experimental MH consists of a generator unit, an inductor unit of ventilator cooling the inductor from outside, an envelope for temperature control maintaining constant conditions in the capsule, and a permanent magnet concentrating and fixing a magnetically controlled drug in the tumor [94]. The envelope for controlling temperature has double walls allowing heat carrier supplied from thermostat to circulate. The capsule, that is, a cylinder manufactured from semi-transparent dielectric material, has openings for discharging urine and supplying air.

A therapeutic device [95] constructed for treatment of the lower parts of the body is comprised of a patient heating unit, a power control unit, and a particle heating unit to heat MNPs inside the patient. The patient is heated by an ultrasonic unit for surrounding tissue heating to a temperature, which is not high enough to cause cell death. The second area comprises a hyperthermia area. The particle heating unit is configured to heat any magnetic particles inside the second area, thereby increasing a temperature in the hyperthermia area. The therapeutic device additionally comprises the second control unit for controlling the particle heating unit, which is configured to manage the location of the second area and to receive patient's treatment planning data.

The document [96] reports on delivery of therapeutics by implanted devices controlled by magnetic field. The device consists of a body, an external periphery and a covering, which takes at least a part of the external periphery and includes the following layers in the order from internal to external: the first insulating layer, a layer of a magnetic material with positive or negative magnetocaloric effect of not less than 3K/T, a layer of a sensitive material, which contains an active substance and is capable of holding and controlled release of the active substance, the second insulating layer, permeable for the active substance. The method of controlled drug release consists of implanting the device into the patient and applying magnetic field to release the active substance. The application of the invention makes it possible to increase safety for surrounding healthy tissues when the drug is released.

An apparatus for a ferromagnetic resonance heating [97] comprises a magnetic field source for delivery of a gradient DC magnetic field to the tumor and an energy source to deliver an RF field (100-200MHz) to the tumor. The superparamagnetic particles retained within the tumor at concentrations 0.1-1% are maghemite (γ-Fe_2O_3) based compounds or yttrium iron garnet ($Y_3Fe_5O_{12}$). The invention allows selective heating of a small portion of the tumor while simultaneously maintaining a safe temperature in the remaining portions and in surrounding tissues.

A device for MH [84] consists of a generator of RF electromagnetic fields, an amplifier of this signal, a transmitter of the generated electromagnetic field, and a direct temperature measurement system (Fig. (**3**)). The device is suitable for use with one or more types of MNPs. The latter dissipate the energy of the applied electromagnetic field in the form of heat. It is also possible to directly control the temperature.

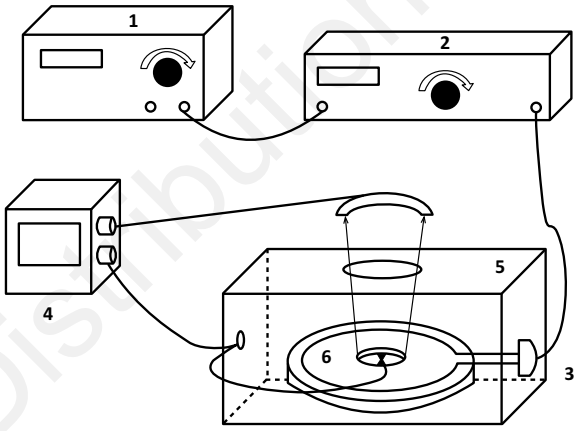

Fig. (3). The device for generating, amplifying and transmitting RF fields for heating of nanoparticles.
Elements are: (1) Generator of RF electromagnetic field, (2) An amplifier of RF electromagnetic field, (3) A transmitter of RF electromagnetic field, (4) System for direct measurement of temperature, (5) A Faraday cage, and (6) Nanoparticles [84].

A magnetic induction therapy device [98] comprises an apparatus body and a medical bed. A magnetic material introduced to the tumor is under the action of high frequency alternating magnetic field. The tumor is heated to 60-70ºC and kept in the required therapeutic temperature range. The magnetic material in the tumor cuts alternating lines of magnetic force to produce alternating current, the magnetic material is warmed up by eddy current, and the tumor is heated.

A heating device using the AC magnetic field (100-750 kHz) applicable for thermotherapy [99] is configured as follows: a ferrite dispersed in an organic substance to be heated and/or is adhered to the surface or inserted into the inside of the organic substance. The ferrite contains at least 50wt% of MgO/Fe_2O_3. The device enables an effective heating of tissue to $\geq$ 45ºC.

The document [100] describes a thermotherapy apparatus, microcapsules and an injectable solution for a low invasive procedure. The MNPs are encapsulated. The device consists of a static section which applies magnetic field to MNPs to concentrate microcapsules at a specified position in the body and increase the time of their stay at that position, and an electromagnetic wave irradiation section which irradiates MNPs. The apparatus may include a section which measures MNP temperature by MRI and a converging section which concentrates magnetic flux in the static magnetic field.

The invention [101] relates to a device that permits the generation of MH by a magnetic field, in such a way that the temperature of MNPs is directly controlled. This can be monitored in order to alter the temperature by means of real-time modifications of the magnetic field. The procedure is controlled by a central processing unit making the process automated.

A system to induce hyperthermia in a selected region of the body [102] consists of permanent magnets mounted on a variable speed motor. A conductive button is positioned at a location proximate to the heated tissue. The magnetic rotor assembly is positioned at a selected distance from the conductive button and rotated at a desired frequency to produce a changing permanent magnetic field that induces an eddy current on the surface of the conductive button. A temperature sensor may be positioned near the conductive button as a feedback mechanism to a control circuit. At higher magnetic polarity frequencies, the conductive button may be implemented in the form of metallic nanoparticles. The nanoparticles may include molecular elements that selectively bind with the target tissue and accumulate in it prior to the introduction of the rotating magnetic field. The system reduces side effects and non-desirable heating and may be controlled in a predictable and repeatable fashion.

CURRENT & FUTURE DEVELOPMENTS

MH emerged as a promising method of local or locoregional treatment of cancer patients. Recent improvements of methods and devices for MH have been focused on rapid and uniform tumor heating and reducing the risk of thermal damage to surrounding tissues (selectivity). Further development of anticancer MH should address yet unresolved problem of heat dissipation across the tumor (see [103] for theoretical considerations). New biomaterials should increase the efficacy of targeting MNPs to individual tumor cells for delivery of heat energy sufficient to kill cells. This key requirement presumes that MNPs remain in the proximity to tumor cells, so that cells are heated for proper time and temperature. If MNP concentration within the tumor is low or they are located not closely enough to tumor cells or washed with blood flow the heating would not reach the threshold necessary for irreversible cell damage. This clinically unfavorable situation is probable since MH is frequently used to treat tumors that acquired multifactorial resistance in the course of natural selection and/or preceding therapy. Therefore, MNPs should be not merely delivered to the target but also retained within the tumor over the period of treatment. This is achievable with external magnetic devices, thereby allowing for control of MNP location and perhaps manipulation with particle distribution to accomplish the uniformity of heat across the tumor.

LIST OF ABBREVIATIONS

AC	=	Alternating Current
HF	=	High Frequency
MH	=	Magnetic Hyperthermia
MNPs	=	Magnetic Nanoparticles
RF	=	Radio Frequency
SAR	=	Specific Absorption Rate
SHF	=	Super High Frequency
UHF	=	Ultra High Frequency

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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