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A REVIEW ON HYPERTHERMIA VIA NANOPARTICLE-MEDIATED THERAPY

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Abstract

Hyperthermia treatment, generated by magnetic nanoparticles (MNPs) is promising since it is tumour-focused, minimally invasive and uniform. The most unique feature of magnetic nanoparticles is their *reaction to* and *manipulation by* a magnetic force which is responsible for enabling their potential as heating mediators for cancer therapy. With magnetic nanoparticle hyperthermia, a tumour is preferentially loaded with systemically administered nanoparticles with high-absorption cross section for transduction of an extrinsic energy source to heat. To maximize the energy deposited in the tumour while limiting the exposure in healthy tissues, the heating is achieved by exposing the region of tissue containing magnetic nanoparticles to an alternating magnetic field. The magnetic nanoparticles dissipate heat from relaxation losses thereby heating localized tissue above normal physiological ranges. Besides thermal efficiency, the biocompatibility of magnetite nanoparticles assists in their deployment as efficient drug carriers for targeted therapeutic regimes. In the present article we provide a state-of-the-art review focused on progress in nanoparticle induced hyperthermia treatments which have several potential advantages over both global and local hyperthermia treatments achieved without nanoparticles. Green bio-nanotechnology has attracted substantial attention and has demonstrable abilities to improve cancer therapy. Furthermore we have listed the challenges associated with this treatment along with future opportunities in this field which it is envisaged will be of interest to biomedical engineers, bio-materials scientists, medical researchers and pharmacological research groups.

Keywords*: Hyperthermia treatment; anisotropy; green bio-nano-technology; infusion rate; magnetic nano-particles.*

1.INTRODUCTION

In oncology, the term *hyperthermia* describes the treatment in which body tissue is exposed to high temperatures (up to 113^{o}F), using an external energy source. Hyperthermia has a long history in the annals of cancer management. A correlation between erysipelas (a streptococcal skin infection) and tumour regression had been observed for over a century before William Coley in 1891 [**1**] first documented evidence of a relationship between infection and cancer regression in sarcoma patients. Ever-expanding research on the hyperthermic treatment of cancer has been sustained over the past four decades [1-12]. In some hyperthermia treatments, the patient's blood is warmed up by an external device before it is re-transfused to the target volume (e.g. isolated limb perfusion and convective whole-body hyperthermia), and those utilizing contact heating (hyperthermic peritoneal and vesical perfusion) [19]. The different approaches are best categorized by the physical mode of power deposition (radiant vs. capacitive vs. convective), and their target volume (local vs. regional vs. whole-body hyperthermia).

Locoregional hyperthermia can be differentiated into external, interstitial and endocavitary hyperthermia. Different heat delivery systems are available: *antennae array*, *capacitive coupled devices* and *inductive devices*. Depending on localization and size of the tumour different methods and techniques can be applied: superficial, intratumoural (thermoablation), deep hyperthermia, endocavitary, and part-body hyperthermia. Randomized clinical trials have been performed mostly with electromagnetic applicators for superficial hyperthermia in combination with radiotherapy, deep hyperthermia, both in the presence and absence of radiation and endocavitary hyperthermia in combination with chemotherapy and radiotherapy. In randomized clinical trials it could be demonstrated, that loco-regional deep hyperthermia with antennae array or capacitive coupled hyperthermia devices may increase response rate, disease free survival and overall survival of patients with cancer in combination with radiotherapy or chemotherapy without increasing the toxicity of standard therapies.

The heating sources are in general practice placed extra-corporally (external to the body) and locally illuminate the tumour region with electromagnetic waves (micro-waves or radio-waves), provided that the tumour location in the respective organ is well located by corresponding imaging techniques (CT, MRI etc). In contrast, whole body hyperthermia is recommended when carcinomas with distant metastases are present. Wust *et. al.* [5] and latter on Hahn [20] and Deatsch & Evans [41] provided details on relevant hyperthermia techniques.

Conductive heating techniques include cavitational water-heating, extra-corporal blood heating and RF needles [18]. The electric properties of each tissue are important in heat delivery methods. In contrast to the ex-vivo based measurements, Balidemaj *et. al.* [24] presented the in vivo conductivity of human muscle, bladder content and cervical tumours, acquired with magnetic resonance-based electric properties tomography (MR-EPT). The temperature-based optimisation was performed with patient models based on conductivity values. Their observations revealed that a higher conductivity in the bladder and in the muscle

tissue surrounding the tumour leads to *higher power dissipation* in the bladder and muscle, and therefore to *lower tumour temperatures*.

The capacitive heating of tumours using a radiofrequency (RF) electric field is a method of hyperthermia, which is however unsuitable for site-specific hyperthermia since it does not allow specific heating of the tumours alone. In capacitive hyperthermia the normal tissue is also warmed in the zone connected to by an electrode. The specific adsorption rate of electric energy depends on electric resistance and permittivity of each tissue type. Since there are no significant differences in the electrical properties of tumour and normal tissues, it is difficult to specifically heat only the tumour. To protect the healthy tissue, mild heating is one option but this approach is often insufficient for treating tumours. To overcome this problem, magnetite cationic liposomes (MCLs) as fine magnetic particles of submicron size in inductive hyperthermia have been deployed by Kobayashi *et. al.* [9, 10]. MCLs were devised in order to improve adsorption by tumour cells and had a ten-fold higher affinity for tumour cells than fine magnetic particles with no electric charge. Kobayashi *et. al.* [11] demonstrated that magnetic nanoparticles serve as a medium that induces efficient heat generation in RF-capacitive heating. In an in-vivo experiment, they observed that heat generation using magnetic nanoparticles was similar to that using inductive heating employing an alternating magnetic field.

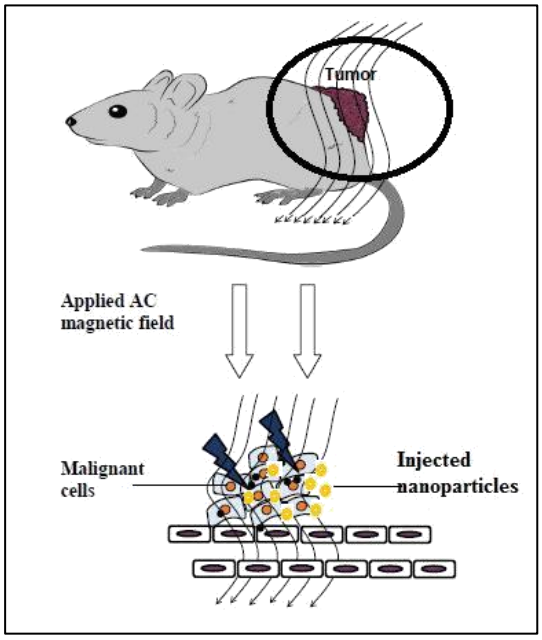

Figure 1: Schematic diagram of hyperthermia treatment.

Therefore with MCL injection, mild hyperthermia generates heat to raise the temperature greater than 108.5^{o}F, required for cancer cell treatment. In contrast, other tissues that have not been injected with MCL do not experience an increase in temperature beyond 108:5^{o}F even if picked up with an electrode. Therefore, magnetic nanoparticles are considered to be a promising heat-generating medium not only for inductive heating but also for capacitive hyperthermia [12].

2. MAGNETIC NANOPARTICLE HYPERTHERMIA

Hyperthermia has not yet been established in clinical routine due to the limitations of the currently available techniques with respect to selectively targeting the tumour region. Magnetic nanoparticle hyperthermia is promising in this regard and can treat the poorly accessible and deep-seated tumours. It has witnessed remarkable development from over two decades ago in 1993, when the group at Berlins Charite Hospital, headed by Andreas Jordan, initiated this field of magnetic fluid hyperthermia [27]. Significant improvement of this methodology has been achieved to date [29, 41, 45]. The schematic diagram in **figure 1** describes the trivial implementation of the magnetic nanoparticle hyperthermia treatment on easily accessible tumours. The concept behind Nanoparticle Hyperthermia Treatment (NPHT) is the MagForce Nanotherapy, which is appealing due to its efficient performance. The nanoparticles extract high energy per applied mass from a magnetic field. Due to their enormous surface [8] the nanoparticles are firstly able to carry a huge number of binding sites for cancer cells/target molecules and secondly able to intrude deeply into tumour tissue. With special coatings, the nanoparticles are delayed by the immune system and thus reach their targets. The nanoparticles can be ingested in great quantities by tumour cells and they can form a homogeneous fluid of low viscosity in water. They also demonstrate bio-compatability. The morphological properties of the nanoparticles, including their size, structure and shape are principally responsible for heat transmission. The nanoparticles are categorized as the multi-domain (with size > 40 nm) and the single-domain particles (with radius << 20 nm). While using *multi-domain nanoparticles*, the heating is delivered by displacements of the domain wall i.e. via hysteresis losses. The single domain particles (often designated 'super-paramagnetic nanoparticles'), on the other hand, induce heating as result of energy loss processes during the re-orientation of the magnetisation in the magnetic field, or frictional losses where the nanoparticle is able to rotate in the surrounding medium, and have thus become commercially more attractive. Hergt *et. al* [21] discussed in detail the physical limitations of the nanoparticle hyperthermia treatment using magnetite fine particles. The specific absorption rate, which actually controls the heating of the tumour cells is defined as the heating potential of the nanoparticles (the amount of heating delivered per unit mass and time as a consequence of the exposure of the nanoparticles to an alternating magnetic field). This important parameter actually dictates the dosages which have to be applied to the tumour region, in order to achieve the inactivation of target cells.

3.DIFFERENT TYPES OF NANOPARTICLES

Different types of biocompatible nanoparticles have been used in the literature. Such particles are directly injected into the tumour tissue, where they are stimulated by an alternating magnetic field to produce heat due to Brownian and Neel (Nobel prize winner in physics in 1970) relaxation processes. Iron-oxide nanoparticles are directly injected into the tumour and release heat after inductively-generated activation by an alternating magnetic field. Superparamagnetic iron oxide nanoparticles (SPIONs) also exhibit excellent biocompatibility in addition to multi-purpose biomedical potential. Iron oxides (either Fe_3O_4 or -Fe_2O_3) can be synthesized through the co-precipitation of Fe2+ and Fe3+ aqueous salt solutions by addition

of a base [14]. The control of size, shape and composition of nanoparticles depends on the type of salts used (e.g. chlorides, sulphates, nitrates, perchlorates, etc.), Fe^{2+} and Fe^{3+} ratio, pH and ionic strength of the media [14, 15]. Fortin *et. al*. [16] presented a comprehensive parametric study for the use of anionic colloidal nanocrystals to generate magnetically-induced hyperthermia. Folate-conjugated superpara-magnetic maghemite nanoparticles have been synthesized for the intracellular hyperthermia treatment of solid tumours and their qualitative and quantitative determinations have been conducted by Sonvico *et. al.* [17].

Gold nanoparticles have been extensively used in the literature for the hyperthermia treatment. Gold has high atomic number which enhances the effect of radio-therapy which is further induced by laser hypothermia. One of the recent developments is the use of colloidal solutions of bifunctional luminescent neodymium (Nd^{3+}) ions doped -$NaYF_4$ colloidal nanoparticles [22]. These particles may be excited in the visible or near infrared range. The infrared excitation is compatible with the windows of biological tissues and achieves sufficient penetration depths compared with either visible or UV-ranges. This characteristic is also coupled with long luminescence times (up to 150 s). Optimisation at 95^{o}F was achieved in 25 % Nd^{3+}:$NaYF_4$ solution. The work reported in [22] has the potential to develop therapeutic agents which could be deducted by molecular agents. Gold nanoparticles coated with biological agents permeate the tumour cells and localize with endosomes. The lower pH within the endosome allows an easy passage for the drug release into the target area.

Magnetite cationic liposomes (MCLs), one of the groups of cationic magnetic particles, can be used as carriers to introduce magnetite nanoparticles into target cells since their positively charged surface interacts with the negatively charged cell surface; furthermore, they find applications in diverse hyperthermic treatments [9, 11, 13].

Figure 2: Superparamagnetic particles under the influence of an external magnetic field (left pannel), without the impact of magnetic field (right pannel). *With permissions from chemicell GmbH [51]*.

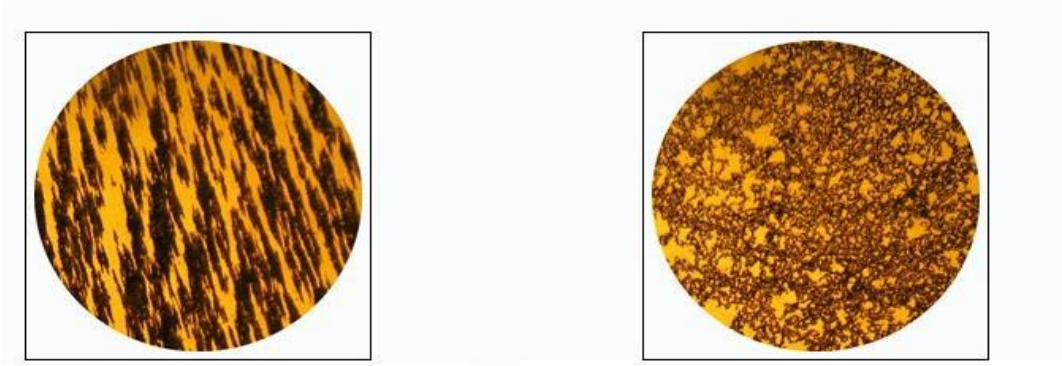

Figure 3: Ferromagnetic particles under the influence of an external magnetic field (left pannel), without the impact of magnetic field (right pannel). *With permissions from chemicell GmbH [51]*.

Magnetite nanoparticles conjugated with antibodies (antibody-conjugated magnetoliposomes, AMLs) have enabled tumour-specific contrast enhancement in MRI via systemic administration. Since magnetic nanoparticles are attracted to a high magnetic flux density, it is possible to manipulate cells labelled with magnetic nanoparticles using magnets. The research group led by Kobayashi developed MCLs as mediators of intracellular hyperthermia. The cationic liposomes adopted by the research group [35] exhibited improved adsorption and incorporation into tumour cells, and had ten times higher affinity for tumour cells than neutrally-charged magnetoliposomes [9]. The applications of these functionalized magnetic nanoparticles with their unique features will further improve medical techniques.

Carbon or polymeric nanoparticles labelled with fluorine-18 deoxyglucose have been studied in pre-clinical models to enhance tumour diagnosis and detection rates using positron emission tomography [26, 25]. Single walled carbon nanotubes (SWNTs) have a wide dynamic range of electromagnetic absorptions that arise from their one-dimensional structure which consists of a honeycomb pattern of carbon that is rolled into a seamless cylinder forming a thin cylindrical form of carbon. The conductivity of carbon nanotubes is determined by the crystalline arrangement of carbon of the cylindrical wall. Nanotubes are either metallic or semiconducting depending on the twist in the graphitic carbon wall. The absorption characteristics of carbon nanotubes have been utilized as hyperthermic enhancers using NIR absorptions by Kam *et. al.* [30]. The synthesis of the above-mentioned magnetic nanoparticles (MNPs) has attracted much attention during the last few years and a list of efficient routes to attain shape-controlled and highly stable magnetic nanoparticles with narrow size distribution has been recently reported by Majidi [31]. Several popular methods including co-precipitation, micro-emulsion, thermal decomposition, solvothermal, sonochemical, microwave-assisted, chemical vapour deposition, combustion, carbon arc, and laser pyrolysis, for the synthesis of magnetic nanoparticles have been discussed with detailed references. Figure 4 describes different routes for the synthesis of silver nanoparticles (AgNP).

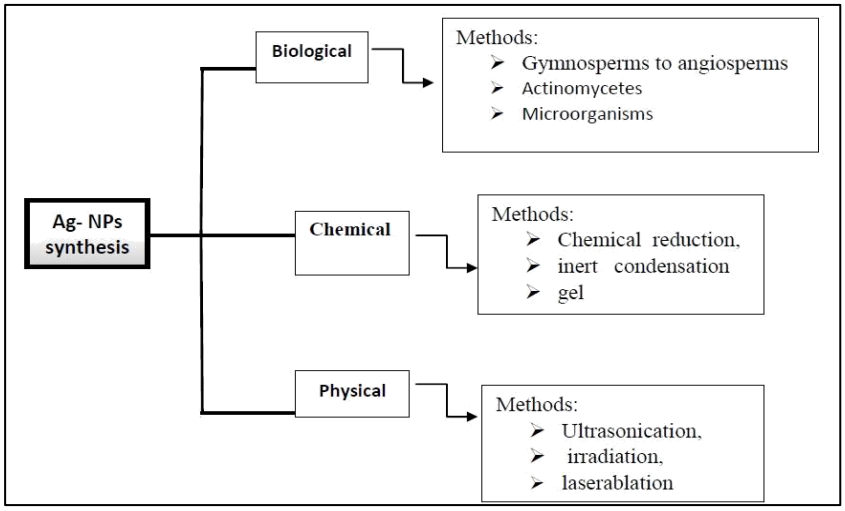

Figure 4: Different routes to synthesis of nanoparticles

Green nanotechnology has also stimulated considerable attention and includes various processes which reduced toxicity. The biosynthesis of metal nanoparticles by plants is currently under development. Biological methods of nanoparticle preparation using micro-organisms, enzymes, fungi and plants or plant extracts are several possible substitutes to chemical and physical methods. Considerable progress in this direction has been made and summarised by Majidi [31], Iravani [32], Yew *et. al.* [33] and the references listed therein. Green synthesis has many advantageous features for the fabrication of magnetic nanoparticles.

4. EXPERIMENTAL/THEORETICAL MODELLING STUDIES OF MAGNETIC NANOPARTICLE HYPERTHERMIA

Controlling both the heat distribution and temperature elevations is an immense challenge in clinical applications of magnetic nanoparticle hyperthermia. Researchers from the USA [36] have evaluated the magnetic nanofluid transport and heat distribution induced by commercially available magnetic nanoparticles injected into the extracellular space of biological tissue using agarose gel with porous structures similar to human tissue. The nanofluid distributions in the gel were examined via digital imaging of the nanofluid spreading in the gel. A radio-frequency electromagnetic field was applied to the gel and thus the nanofluid injection and the initial rates of temperature rise at various locations were measured to obtain the specific absorption rate (SAR) distribution. This experimental study provided a benchmark towards providing guidance for designing better treatment protocol for future improved hyperthermia treatments. In 2007 the group headed by Jordan [49] reported the results of the first study into the feasibility of magnetic fluid hyperthermia in human patients. Their study involved 14 patients receiving treatment for a particularly severe type of brain cancer, recurrent "*glioblastomamultiforme*", via a combination of fractionated external beam radiotherapy and several sessions of thermotherapy. Thermotherapy was effected by heat generated from aminosilane coated iron oxide nanoparticles that had been injected into multiple sites throughout each tumour. The choice of injection sites was based on data from a

comprehensive series of MRI scans of the cranium coupled with a specially developed software planning system (NanoPlan). The superparamagnetic iron oxide nanoparticles (core size 15 nm) were dis-persed in water at a concentration of 112 mgFe ml. Each tumour was injected with from 0.1 to 0.7 ml of the magnetic fluid per ml of tumour and then exposed to a magnetic field of 3.8 to 13.5 kAm1 alternating at 100 kHz. The study successfully demonstrated that this form of thermotherapy using magnetic nanoparticles could be safely applied to the treatment of brain tumours and that hyperthermic temperatures could be achieved. Very small deposits (0.1 ml) of the magnetic fluid could be precisely deposited within the targeted area. Follow-up CT scans and reproducible temperature measurements confirmed that these deposits were stable over several weeks. Patient survival and local tumour control were not considered primary endpoints of this study, however, clinical outcomes were observed to be promising with the therapy being well tolerated by all patients. More complete evaluation of clinical outcomes is to be assessed in a phase II study on 65 patients with recurrent glioblastoma multiforme. Later on, the research group headed by Jordan applied their methodology for the treatment of prostate cancer [28, 37]. An overview on their findings is provided in **Table 1**.

Considerable efforts have also been made in recent years to optimize material properties for magnetic hyperthermia applications [46, 47]. Due to the complexity of the problem, several aspects pertaining to the combined influence of different parameters such as those associated with the geometry, concentration and absorption rate of the nanoparticles and the period of thermal ablation of tumour cells, are still unclear. Recently, Verde [50] *et. al* discussed in detail the role of the magnetic anisotropy on the specific absorption rate of cobalt-ferrite nanoparticles with diameters < 14nm. They demonstrated that the anisotropy is in fact a prime parameter in the search for materials optimized for magnetic hyperthermia. X-ray diffraction was used for carrying out the structural characterization. The relevant magnetic parameters were extracted from vibrating sample magnetometry. Hyperthermia investigations were performed at 500 kHz with a sinusoidal magnetic field. The specific absorption rate was investigated as a function of the coercive field, saturation magnetization, particle size, and magnetic anisotropy. The theoretical predictions from the linear response theory and dynamic hysteresis simulations were validated by experimental findings achieving close agreement in both cases.

Superparamagnetism is a form of magnetism, which appears in small ferromagnetic or ferrimagnetic nanoparticles. Deep understanding of magnetic relaxation phenomena of the superparamagnetic iron oxide nanoparticles (SPIONs) has become a challenge due to their importance in pharmaceutical and industrial communities. The precise control of the physiochemical properties of these magnetic systems is crucial for hyperthermia applications, as the induced heat is highly dependent on such properties. Jordan *et. al.* [48] discussed in detail the limitations and recent advances in the development of superparamagnetic iron oxide nanoparticles for hyperthermia. Egli [47] provided a useful comparison for the analysis of SPIONs and provided a self-consistency check of existing theories on magnetic relaxation phenomena using the susceptibility inversion. The physical, magnetic and heating characteristics of magnetite nanoparticle suspensions with average diameters of 12.5 and 15.7

nm were discussed in detail by Suto *et. al* [53]. They highlighted the relative contributions of Neel and Brownian relaxations on magnetic heat dissipation and reported that the specific absorption rates (SAR) dropped by 27% for the 12.5 nm particles and by 67% for the 15.7 nm particles, by suppressing the particle rotation (via dispersion of magnetite nanoparticles in hydro-gel).

Recently a research group led by Sinibaldi [44] provided a quantitative framework to demonstrate *nanofluid infusion* and the subsequent thermal activation of the infused nanoparticles for hyperthermia treatment. A simplified analytical technique was adopted to predict the nanoparticles concentration profile during the infusion process. The concentration profile was then exploited to depict the steady-state temperature profile. Despite the simplifications introduced to enable the analytical derivations, their research group claimed to take into account physically relevant aspects including tissue heterogeneity, poroelasticity, blood perfusion and nanoparticle absorption onto tissue. They obtained optimal working curves which could be effectively used for planning real procedures. Another study conducted by the same group provided an analytical expression for the *time-dependent* nanoparticle concentration during the infusion into poroelastic brain tissue, which also accounts for particle binding onto cells [45]. The role of the involved physical aspects was considered including the tissue poroelasticity, infusion parameters and nanoparticles physico-chemical properties. Their model was validated by considering the clinically relevant ranges for the infusion parameters. The research group led by Bellizzi [54] presented the optimisation criterion for the choice of magnetic nanoparticle hyperthermia conditions and later provided the numerical assessment with reference to the challenging and clinically relevant case of brain tumours, by using a 3D model of the human head [55]. The two important features of their study were the minimised magnetic nanoparticles dosage and the controlled temperature rise to enable efficient and safer treatment. Their findings further confirmed that when a magnetic field with high amplitude is used, the most efficient magnetic nanoparticles are those with multi-domain core. A number of seminal investigations from the past three decade have been documented in **Table 1**, along with the nanoprticle type, size, coating, advancement and the drawbacks of the study.

5. CONCLUSIONS

A small rise in tumour temperature with magnetic nanoparticle hyperthermia makes cancer cells more susceptible to radiation and chemotherapy. The means of achieving this is not trivial, and traditional methods have certain drawbacks. Loading tumours with systematically administered energy-transducing nanoparticles can circumvent several of the obstacles to achieve tumour hyperthermia. However, nanoparticles also face unique challenges prior to clinical implementation. This article has summarized the current technologies and described the advantages and challenges of magnetic nanoparticle hyperthermia studies. Infusion duration and flow rate, nanoparticle concentration in the nanofluid, magnetic field intensity and frequency have been identified as the controlling parameters of this challenging treatment. Researchers from different parts of the world are trying to provide generalized criteria which could significantly improve the magnetic nanoparticle hyperthermia performance, by reducing the required magnetic nanoparticle dosage and enabling, at the same time, a complete planning

of the temperature rise of the exposed tissue. The 21st century will inevitably witness continued expansion in magnetic nanoparticle hyperthermia research.

Table 1: Summary of selected studies

References & year	Particles type & size	Coating	Research Type	Findings & Flaws
Jordan *et'al* [34] (1997)	Superparamagnetic magnetite Fe_2O_3/Fe_3O_4 (3-4 nm)	Dextran	Animal clinical studies (Magnetic hyperthermia)	Delays the tumour growth after treatment. Causes unintentional MF-infiltration.
Ito *et'al* [35] (2004)	anti-HER2 immunoliposomes magnetite nanoparticles (138 nm)	- -	Human clinical studies (Tumor-specific hyperthermia)	Applicable to treatment of HER2-overexpressing cancer. Superior hyperthermic effects induced by repeated hyperthermia
Salloum *et'al* [36] (2008)	Polymer encapsulated Fe_2O_3 10 nm	- -	Test tube experiemnt (Magnetic hyperthermia)	Suitable for evaluating magnetic nanofluid transport. Nonunifrom size leading to heating profiles.

Summary of selected studies (contd)

References & year	Particles type & size	Coating	Research Type	Findings & Flaws
Johannsen *et'al* [37] (2010)	Silica-Fe_2O_3 (1-100 nm)	- -	Human clinical studies (Magnetic hyperthermia)	Suitable for thermal ablation of prostate cancer. Lacking direct real-time visual control of the magnetic fluid injection.
Dombrovsky *et'al* [38] (2011)	Silica nanoshells 20 nm (radius)	Gold-coated	Thermal model (Photothermal hyperthermia)	Suitable to obtain thermal regime of long-time soft thermal treatment of specific tumors. Inconsideration of the role (a) metabolic heat generation and (b) blood perfusion.
Branquinho *et'al* [39] (2013)	BNF-starch & MNF-citrate (1-100 nm)	Starch & Citric acid	Theoretical model (Magnetic hyperthermia)	For optimization of chain size and particle diameter. Requires qualitative analysis vs quantitative analysis.
Rengan *et'al* [40] (2015)	LiposAu NPs (5-8 nm)	Gold-coated	Animal clinical studies (Photothermal hyperthermia)	Biodegradable hybrid nanoparticle system for treatment of specific tumors.

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