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LETTER TO THE EDITOR

Hyperthermia classic commentary: 'Inductive heating of ferrimagnetic particles and magnetic fluids: Physical evaluation of their potential for hyperthermia' by Andreas Jordan et al., *International Journal of Hyperthermia*, 1993;9:51–68.

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Abstract
In order to increase the specific power absorption (SAR) in deep seated tumors, the idea was born to use AC magnetic fields in combination with magnetic particles instead of conventional E-field dominant systems. It was found, that nanoscaled particles were superior to micron-sized, multi-domain particles in terms of SAR due to different mechanisms how the field energy is converted into heat. Crucial parameters were identified for the human application of the method, such as the AC magnetic field amplitude and frequency, the nanoparticle composition and size distribution. Based on these physical and chemical relationships, a new thermotherapy method has been developed to heat up deep regional tumors using aqueous dispersions of iron oxide nanoparticles (magnetic fluids). Several clinical studies were initiated using this new heating technology. The results of the most advanced efficacy study for recurrent glioblastoma multiforme patients in combination with conventional radiation therapy are expected at the end of this year, 16 years after publication of this fundamental paper.

Keywords: *thermotherapy, magnetic fluid hyperthermia, nanoparticles, nanotechnology*

The above mentioned paper [1] was the result of many years of research about the problem of how to enhance the specific power absorption (SAR) in deep-seated tumours. In the late 1980s, I observed many clinical deep regional hyperthermia treatments with annular phased array systems (APAS) in the Radiation Oncology Department of Peter Wust at the Charité University of Medicine, Berlin. I got the impression that the power absorption at the surface of the body was too high in comparison to the SAR within the tumour. Further steering problems of the power deposited due to the different electrical properties within the target tissue largely restricted a homogeneous heating of the tumour [2]. From numerous preclinical work with cells and animals it was well known that the inactivation of tumour cells is strongly dependent on the thermal dose [3]. Based on these observations the idea was born to use AC magnetic (H) fields instead of E-field dominant

systems in order to enhance the loco-regional SAR. The power absorption of electromagnetic fields within lossy medium is quite similar, but using H-fields, energy absorbing materials could be used to target the heat and would be independent of the electrical properties of the tissue. I found several basic observations and equations from the early work of Brezovich et al. [4, 5], Oleson et al. [6, 7] and Stauffer et al. [8, 9], who investigated the effects of H-fields alone and together with ferromagnetic thermoseeds for hyperthermia. But there were also restrictions with this technique: the necessity to surgically implant each seed into the target tissue and the critical orientation of each seed according to the axis of the externally applied magnetic field.

Based on these recognised limitations, ferro- or ferromagnetic particles could also be used which might be applied as an aqueous dispersion into the tissue, which would be much easier to implant

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compared to seeds. Several groups had already done those experiments albeit with animals using very different applicators, frequencies, field strengths and temperature measurement methods [10–21]. In terms of a probable patient application, there were no systematic investigations of which frequencies and field strengths could be used in larger bodies than laboratory animals. Based on the earlier investigations of Brezovich [4, 5] and Oleson [6, 7], the eddy current power absorption increases to the square with the radius of the body, the magnetic field strength, the frequency and the conductivity. We measured the power absorption of different ferro- and ferrimagnetic particles in terms of dependence on frequency, field strength and particle type. Using micron-sized multidomain particles we needed large field strengths (> 6 kA/m) to obtain a reasonable heating of the particles. Under consideration of a tolerable SAR through eddy current heating in the range of 25mW/mL observed with conventional APAS, we could estimate which field-frequency combinations would be applicable using those particles and which SAR we would need to get more than the eddy current heating (at maximum radius) into the tissue.

I truly remember the day in summer of 1990, when we measured for the first time the SAR of a dispersion of nano-sized iron oxide particles. As we had done hundreds of measurements with different ferrite particles embedded in agar to circumvent sedimentation of the particles within the sample vial, this time we took a so-called magnetic fluid, a stable dispersion of nano-scaled iron oxide particles coated with a dextran shell. After a few minutes with the same high magnetic field amplitude we had used in all measurements before (12 kA/m), the plastic tube suddenly exploded and the black liquid splashed through the room and on our cloths. After we had excluded any errors from our experimental set-up, we noted that nanoscaled particles, i.e. subdomain particles (SDP) were superior to micron-sized, multidomain particles (MDP) in terms of SAR. As a mechanism we postulated that Neél and Brown relaxation of SDP would produce much more energy than hysteresis losses from multidomain particles at clinically applicable magnetic field conditions.

Today we know much more about these physical mechanisms, which were published later in large number of publications [22–31]. It has been confirmed that the choice of field amplitude and frequency is crucial for the power absorption obtained. But a much more critical parameter is the nanoparticle size distribution. A maximum power absorption may be expected by preparation of particle suspensions with narrow size distribution and with a mean diameter that corresponds to the maximum coercivity in the single domain size range.

In the optimum case the field amplitude is large enough to exceed the coercivity of most of the particles within the dispersion. A still insufficiently understood issue is the magnetic particle interaction (i.e. in the form of particle cluster), which may have a strong influence on power absorption [32]. Different bottom-up synthesis approaches have been reported to obtain a narrow size distribution [33] or to magnetically fractionate dispersions of broader particle distributions [34, 35]. From the relaxation theory, saturation magnetisation of the particles is a further important parameter of power absorption. For example, one of the highest saturation magnetisations has been reported with ferromagnetic cobalt nanoparticles (Fe_3Co) [36]. Extremely large power absorption can be achieved with those composite ferrites, but critical issues arise from the toxicity profiles of those particles, which are not known so far. Just these elements, such as cobalt, manganese and nickel, which hold promise from the physical point of view, are critical in terms of toxicity and have to be examined carefully before application in cancer treatment.

Since our very basic physical paper in 1993, a huge number of papers have been published describing numerous effects of iron oxide nanoparticles in the thermotherapy of cells, tissues and animals, which cannot all be mentioned here. One important conclusion is that iron oxide nanoparticles activated through an alternating magnetic field are able to inactivate cells and tumours in a dose-dependent manner, which is comparable to other heating methods. However, this statement is only true if the particle distribution or the particle deposits after interstitial application are almost homogeneously distributed throughout the target tissue, which is still the highest challenge in clinical application. The problem of steering the field using conventional E-field dominant systems is exchanged here for the problem of nanoparticle target application, which seems to be not much easier. To obtain full control of the target volume SAR, the particle distribution and concentration throughout the target region should be well known for a given frequency field strength combination of the magnetic field. Since iron oxide nanoparticles are incompatible with MRI, other methods must be chosen to estimate the particle distribution. A practical approach is computed tomography (CT), which allows the quantitative detection of the particle deposits by means of differences in Hounsfield units [37].

A specific issue with thermotherapy using magnetic nanoparticles is temperature measurement and control. Although magnetic particle concentration (estimated by CT scan) and particle SAR are well known for a given field frequency combination, the inhomogeneity of particle distribution causes large

thermal gradients between particles and particle deposits within the tumour tissue. Therefore it is not surprising that conventional invasive temperature measurements using e.g. fibre-optic probes are extremely sensitive to the position of the probe within the thermometry catheter. After the interstitial application of the nanoparticles, post-implantation analysis (PIA) is used to verify the particle distribution and concentration throughout the tumour [37]. Any dislocation or kink of the thermometry catheter leads to a dislocation of the temperature measurement and therefore to inaccurate temperature data in comparison to the calculated values.

Recently a new temperature measurement method has been published which uses the ratio of the fifth and third harmonics of the magnetisation generated by magnetic nanoparticles in a sinusoidal field to generate a calibration curve and to subsequently estimate the temperature with an experimentally determined accuracy of $0.3°K$ between $20°$ and $50°C$ [38]. However, the sensitivity of the method in terms of aggregation of the nanoparticles, viscosity and binding of the particles at the target size are open questions which will largely influence the applicability of the method beside the challenge to implement such a coil system into clinical AC magnetic field applicators (e.g. MFH®300F, MagForce Nanotechnologies AG, Berlin, Germany [37]). A further approach to solve the temperature measurement problem is the carbon nanotube (CNT)-based medical system developed by Klingeler and his group [39]. The filling of CNTs with magnetic materials offers the potential for hyperthermia applications while the insertion of NMR active substances allows the usage of markers and sensors. Hereto, many alkali and cuprous halides are known to show pronounced temperature dependencies of NMR parameters. The authors demonstrate the proof of concept by using monovalent cuprous iodine, with which they filled the CNTs. The accuracy they achieved with this system was $2°K$ by means of the spin-lattice relaxation measurement.

A further line of development comprises the conjugates or surface coatings of iron oxide particles with drugs for temperature-sensitive drug release, which might become a parallel pathway to the well known and clinically applied temperature-sensitive liposomes. Using all the complex surface chemistry on nanoparticles, almost all modifications can be applied depending on the particle surface structure and reactants in a colloidal system [29, 40, 41]. The nature of surface coatings and their subsequent geometric arrangement on the nanoparticles determine not only the overall size of the colloid but also play a significant role in the biokinetics and biodistribution of nanoparticles in the body. Magnetic nanoparticles can bind to drugs, proteins,

enzymes, antibodies and nucleotides, and can be directed to an organ, tissue or tumour using an external magnetic field [42, 43].

Despite numerous activities in research and development, our group started the first clinical studies in 2003 with thermotherapy using magnetic nanoparticles [44] and the first clinically approved magnetic therapy system [37]. The clinical observations so far depict clearly both the potentials and the limitations of method: with recurrent glioblastoma multiforme, patients' high magnetic field amplitudes are highly tolerable up to 9 kA/m in comparison to the 10–15 kA/m we calculated from our theoretical considerations (Figure 8 [1]). At maximum body cross-section, 4 to 4.5 kA/m can be applied to patients with a frequency of 100 kHz instead of 6 kA/m in comparison to the calculated SAR (Figure 7 [1]).

Thermotherapy using magnetic particles: Current status

Pros:

- Selectively alters targeted tumour tissue; normal tissue is spared ('intrinsic heating')
- Highly tolerable therapy if eddy current heating is considered through a safe applicator and a conservative frequency field combination
- Is minimally invasive (interstitial injection of the particles into the tumour), all further therapy steps are contactless from outside
- Can be repeated over several weeks up to months if the particles form a stable deposit within the tumour tissue
- The treatment can be planned three dimensionally using conventional DICOM data
- The calculation of the expected heating can be done by CT-based post-implantation-analysis (PIA)
- Is suitable for hyperthermia and thermoablation applications

Cons:

- Difficult to homogeneously distribute the particles intratumourally by interstitial application
- Limited magnetic field strength applicable (≤ 4.5 kA/m, 100 kHz) for abdominal tumours
- High thermal gradients
- Direct temperature measurements are required initially
- Loco-regional therapy, not suitable for disseminated tumours
- Target size limited to approximately 100 cm^3

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In summary, our paper republished in the *International Journal of Hyperthermia* was the start of a new technology to heat tumours using magnetic nanoparticles. The physical potential of nanoscaled iron oxide nanoparticles with extraordinary high power deposition was reported in a systematic investigation, and more importantly, in the context of patient applicable frequencies and magnetic field amplitudes of an alternating magnetic field. Numerous papers of other authors and our group followed this paper introducing nanotechnology into thermotherapy in general. Starting from this basic physical concept, chemical synthesis of nanoparticles was inspired in view of this application. Numerous biological investigations were made with cells and animals to describe all these new biological effects. Several clinical studies were initiated using this new heating technology. The results of the most advanced efficacy study (phase II) for recurrent glioblastoma multiforme patients in combination with conventional radiation therapy are expected at the end of this year, 16 years after publication of this fundamental paper.

Declaration of interest: Andreas Jordan is CSO of MagForce Nanotechnologies AG.

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