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Opinion

Translational Hurdles with Magnetic Nanoparticles and Current Clinical Scenario in Hyperthermia Applications

Raghvendra A. Bohara [1,2,*] and Stefano Leporatti [2,*]

[1] CÚRAM SFI Research Centre for Medical Devices, University of Galway, H91 TK33 Galway, Ireland
[2] CNR Nanotec-Istituto di Nanotecnologia, 73100 Lecce, Italy
* Correspondence: raghvendrabohara@gmail.com (R.A.B.); stefano.leporatti@nanotec.cnr.it (S.L.)

Abstract: Magnetic Nanoparticles (MNPs) are becoming increasingly popular for biomedical imaging and drug delivery, particularly cancer theranostics. Due to their excellent inherent properties and the accessibility to be tailor-made according to specific requirements, they stand out from the crowd and are close, yet so far. While the number of publications related to MNPs' drug-delivery systems reported in the literature increases yearly, relatively more minor conversion has been observed from the bench to the bedside. It is of paramount importance to understand and work on the shortcomings and redesign the strategies to increase the clinical translatability of MNPs. 'Supply as per Demand' should be followed while designing an MNP-based delivery system. To achieve this, a better understanding of the clinical issues should be addressed early, and downstream methods should be prepared to resolve them. More significantly, all clinical problems in one delivery system should be eliminated, and one problem and one solution should be pursued. This opinion review explores the current limitations in evaluating magnetic nanoparticle performance, suggesting a promising standardized pathway to clinical translation.

Keywords: magnetic nanoparticles; hyperthermia; heat; cancer

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1. Introduction

Magnetic nanoparticles (MNPs) are increasingly being considered for several biomedical applications due to their inherent ultra-fine size, biocompatibility and superparamagnetic properties [1]. The functional properties of the MNPs can be tailored for specific biological functions, such as drug delivery, hyperthermia or magnetic targeting, Magnetic Resonance Imaging (MRI), cell labelling and sorting, and immunoassays [2]. Among the different MNPs, iron oxide nanoparticles (maghemite γ-Fe_2O_3 or magnetite Fe_3O_4) are popular formulations. The applicability of iron oxide nanoparticles depends upon nanoparticle size, functionality, stability, dispensability, interfacial surfaces and superparamagnetic properties [3]. Magnetic metal oxide nanoparticles are a significant class of nanoscale materials with the potential to revolutionize current clinical diagnostic and therapeutic techniques, mainly in cancer therapeutics [4]. Due to their unique physical properties and ability to function at the cellular and molecular level of biological interactions, MNPs are actively investigated in MRI contrast agents as carriers for targeted drug delivery [5]. Several MNP formulations have broad applications in detecting, diagnosing, and treating illnesses such as cancer, cardiovascular disease, and neurological disease [6]. MNP may soon play a significant role in meeting the health care needs of the future. Figure 1 describes the number of publications in the Scopus database in the last two decades related to magnetic nanoparticles and cancer. It is phenomenal to see a rise in the trend of articles, but inevitably there seems to be a lack of translation of articles into products. Table 1 discusses the advantages and pitfalls of magnetic nanoparticles for Magnetic Fluid Hyperthermia (MFH) therapy.

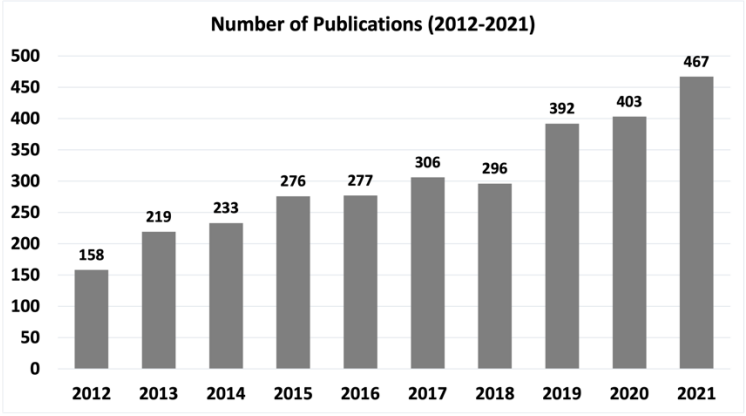

Figure 1. Magnetic nanoparticle publications in Scopus as of December 2021.

Table 1. Advantages and pitfalls of magnetic nanoparticles for MFH therapy.

Advantage	Improvement Required
As theranostics	Improvement in large-scale synthesis techniques
Improved Biocompatibility and Biodegradation	Development of simple functionalization techniques with the use of biodegradable materials
Targeting ability	The detailed understanding of immune interaction is required
Manipulated by Magnetic Field	Batch after Batch reproducibility

Using nanotechnology, the proposed plan for hyperthermia was refurbished. This started when Gilchrist et al. initially started magnetic hyperthermia (MHT) by exposing various tissues (dogs) to an alternating magnetic field (AMF) with magnetic particles relatively larger in size used (>100 nm) [7]. Later, researchers used Fe_3O_4-coated dextran for cancer treatment on rats bearing mammary carcinomas in an in vivo study [8]. The first clinical trial of MFH was performed on patients with prostate carcinoma at Charité Hospital in Berlin, Germany, jointly with MagForce in 2006. While subsequent clinical trials are ongoing on chondrosarcoma, cervical carcinoma, prostate carcinoma, ovarian carcinoma, glioblastoma multiforme and rectal carcinoma [9–11], the readers are directed elsewhere for further reading on clinical trials.

2. Technical Challenges

Despite the initial success, the therapy was never established in the clinical setting [10]. The possible technological challenges associated with MFH are technical and pointwise, as described below. Readers are encouraged to note these points while designing any new research on MNPs, which will help them find a possible solution to the challenges associated with this approach.

1. Generally, the heat dissipation of available commercial magnetic (NanoTherm) fluids within a physiologically safe range of alternating MF is insufficient for the complete eradication of tumours [11,12].
2. A specific absorption rate (SAR) is the key indicator for evaluating the efficiency of any magnetic fluid. One hypothesis suggests that an SAR close to 1000 W g^{-1} at a fluid concentration of 5 mg mL^{-1} may be adequate. It has to be noted that the SAR depends upon intrinsic and extrinsic properties of the fluid [13–16]. Higher heating efficiency would be highly desirable as it would reduce the number of nanoparticles, field strength and frequency required to induce significant heating [17].
3. Protein corona engulfment by macrophages is one of the leading causes of failure in clinical settings. It has to be noted that the aggregations of MNPs form large clusters, which are easily detected by the reticuloendothelial system (RES) of the host body [18].
4. On-site delivery of the particles to overcome technical limitations will be discussed. Ideally, a high concentration of MNPs (and subsequent high heating effect) should

be localized at the tumour and not accumulate in healthy tissues. In reality, this is seldom the case [3]. Still, the low availability of MNPs and fluid diffusion into the surrounding tissue is observed.

5. Irrespective of the injection procedure, applied MNPs uniformly designed with cell-specific identification fractions (i.e., antibodies, proteins) somehow make their way to off-target excretory organs (spleen, liver, or kidneys). As validated in preclinical animal trials and MFH clinical settings, this results in side effects such as secondary heat damage to healthy tissues [19].
6. Another major technical challenge is the lack of control in the real-time monitoring of temperature rise during treatment. This is because MNPs are heated in a non-uniform manner, depending on their location in the tumour [7]. Randomly oriented accumulation of magnetic fluid within the tumour allows for comparatively significant temperature variations during the application of MFH as measured by temperature measurement using invasive thermal sensors.
7. Patients withstand lower magnetic field strengths during therapy. However, higher magnetic field values have been reported to cause pain in the perineal area or groin, burning sensations, and increased skin irritation due to the development of hot zones [20].
8. In addition, official studies on the actual achieved clinical temperature of the tumour cells measured by invasive thermometry differ considerably by several °C, evaluated by the temperature expected by the bioheat transfer equation resulting from the treatment outcomes.
9. The lack of standard measurement protocols, the standard composition of fluid concentration and different reported SAR/SLP values create lots of ambiguity [14].

3. Proposed Criteria to Maximize the Efficiency of MFH

The injected magnetic ferrofluid should meet specific criteria to qualify as an optimal heating mediator for MFH.

1. The first and foremost criteria are to generate maximum temperature and SAR/SLP values with a low quantity of fluid at biologically benign field (f, H) values to minimize the potential side effects [7].
2. Secondly, NPs should possess high size uniformity and zeta potential values to favour homogeneous heat dissipation inside the tumour. For this, a robust and straightforward synthesis method should be developed to produce bulk and homogenous synthesis of MNPs [21].
3. Doping with diamagnetic material or other similar relevant kinds of materials can be a vital strategy to increase the magnetic susceptibility, high Ms, high magnetic anisotropy constant, super-paramagnetism and biocompatibility [22,23].
4. Designing the core–shell structure can be a vital strategy to increase SAR/SLP values with a low quantity of fluid at biologically benign field (f, H) values to minimize the potential side effects.
5. Additionally, magneto-tactic bacteria (MTB), metal-doped spinel ferrite, magnetic–plasmonic multifunctional nanohybrids optically active in the NIR region, and self-controlled MFH, have also been studied with outstanding outcomes.
6. A more relevant organoid model should be designed for better performance tracking, preventing rapid and more accurate therapeutics and avoiding later stage failure.

4. Feature Outlook

Improving the inherent properties of MNPs by attenuating their morphology, scale, particle size, crystalline nature, and compositional shaping has shown an exciting ability to enhance the healing ability of MNPs. The problem with ongoing field experiments is the uncertainty of the challenges in determining the concentration of fluid and MF variables used. This variance made it hard to compare the reported data. Standardization is thus necessary for the research community to operate under the same experimental conditions and under

scientifically defined alternating MF conditions. In addition, sophisticated instrumentation and high-performance technology are necessary to optimize the concentration of MNPs in tumour areas and increase MF's focus specifically on tumours. Considering the modest marginal increase in SAR/SLP values over the last several generations, it is questionable that many orders of magnitude improvements in SAR/SLP values will be accomplished.

Immunological safety is another crucial factor to consider. While the extant literature contains methods, techniques, and approaches for studying the immunological safety of prospective MNPs, the standard process concentrates on macrophages and monocytes, which serve as the immune system's first line of defence. However, there is a lack of fundamental research that can assist us in comprehending how MNPs impact the long-term immune response and distinct types of immune cells.

Therefore, the goal should be to calculate the highest permissible magnetic field for MFH treatment and enhance the position of engineered MNPs in systemic cancer delivery. Chemists, physicists, biologists, and clinicians need to work closely together in a joint research project to achieve the ambitious goal of successful clinical application of MFH in the near future.

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