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Magnetic Nanoparticles: Biomedical Applications and Challenges

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Abstract: ***The progress in the development of magnetic nanoparticle based therapies for various biomedical applications is reviewed here. Most significantly, magnetic nanoparticles have been widely used in drug delivery and hyperthermia treatment for cancer. However, recent applications of magnetic nanoparticles demonstrate their promise towards decreasing implant infection and increasing tissue growth. To build the most effective magnetic nanoparticle systems for various biomedical applications, particle characteristics including size, surface chemistry, magnetic properties and toxicity have to be fully investigated. In this review, several new applications of magnetic nanoparticles in the medical arena as well as remaining challenges for such clinical use are discussed.***

Keywords: Magnetic Nano particles; Applications in Biomedical Research; Hyperthermia;Tissue repair; Challenges;Toxicity of Nano particles.

1. Introduction

In recent years, nanometre particles have drawn a great deal of interest from the biomedical research world. Nanoparticles with sizes less than 100 nm possess unique properties (such as high surface-volume ratios, high reactivities, etc.) compared to their bulk micron-structured counterparts due mainly to size effects and surface phenomena at the nanoscale. Magnetic nanoparticles are particularly promising in several biomedical applications, such as: (a) cellular therapy involving cell labeling and targeting and as a tool for cell-biology research to separate and purify cell populations; (b) tissue repair;(c) targeted drug delivery; (d) magnetic resonance imaging (MRI); (e) hyperthermia for cancer treatment; etc.

For more effective therapeutic treatments, materials with highly saturated magnetization (such as transition metals (e.g. Fe, Co, Ni) or metal oxides (e.g. Fe3O4, g-Fe2O3) are usually considered. Although pure metals possess the highest saturation magnetization, they are highly toxic and extremely sensitive to oxidation therefore, without a further appropriate surface treatment such pure metal nanoparticles are not relevant for biomedical applications.In contrast, iron oxides are less sensitive to oxidation and, therefore, can give a stable magnetic response. In fact, small iron oxide nanoparticles have been applied to in vitro diagnosis for about 50 years. Recent studies have demonstrated that magnetite (Fe3O4) and maghemite (g -Fe2O3) are very promising candidates due to their biocompatibility and relative ease to functionalize (for example with polymers such as dextrant, polyethylene glycol (PEG), polyvinyl alcohol (PVA) or functional groups such as thiols, amines and carboxyls) for a wide range of applications For practical purposes, these nanoparticle surfaces must be tailored to improve biocompatibility properties and reduce aggregation. Without any surface modification, magnetic iron oxide nanoparticles possessing hydrophobic surfaces with large surface area to volume ratios tend to agglomerate and form larger clusters, resulting in increased particle sizes. These agglomerations have strong dipole–dipole interactions and ferromagnetic behaviour.Clusters will be further magnetized when in a magnetic field, causing a stronger attraction between the magnetic nanoparticles and consequently, creating increased aggregation. Moreover, nanoparticles with proper surface coatings to avoid such agglomerations can stay longer in circulation and are less recognized by the body's biological particulate filters, such as the reticulo-endothelial system (RES) which is a part of the immune system that consists of the phagocytic cells located in the reticular connective tissue.Magnetic nanoparticles can be functionalized with organic materials (e.g., polymers such as dextrant40 and polyethylene glycol (PEG) or inorganic metallic (e.g., gold) or oxide (e.g., silica or alumina44) materials to achieve desirable dispersibility. In all cases, magnetic nanoparticles less than 15 nm in diameter are of interest because they exhibit superparamagnetic properties, meaning that they do not retain any magnetism after removal of a magnetic field and can avoid the RES.

Iron oxide magnetic nanoparticles can be preparedby several different methods including co-precipitation, thermal decomposition and/or reduction, micelle synthesis, hydrothermal synthesis, and laser pyrolysis techniques. A more extensive review can be found in the work by Tartaj et al. and Lu et al. The aim of this review article is to provide information concerning new applications of magnetic nanoparticles in biomedical research as well as the challenges they have to overcome before experiencing wide spread clinical use.

2. Applications of Magnetic Nanoparticles in Biomedical Research

2.1 Drug delivery

One of the most desirable applications for magnetic nanoparticles is targeted drug delivery to fight cancer, where nanoparticles are functionalized with appropriate groups (such as (poly (methyl methacrylate) or PMMA, PEG, etc.) loaded with drugs (carboplatin, doxorubicin, paclitaxel, 5-fluorouracil, epirubicin, etc.) and directed to and focused at tumour sites by an external magnetic field. For these applications, the size, surface chemistry, and charge are particularly important to ensure that the

nanoparticles can stay for a long time in circulation. It is believed that magnetic nanoparticles with sizes ranging from 10 to 100 nm are most suitable for drug delivery applications. The lower threshold is based on the fact thatparticles smaller than 10 nm are easily removed by extravasation and renal clearance.The upper threshold is not well defined, however, some recent data suggest that nanoparticles 50–100 nm are smaller than the spleen cut off (200 nm) and can penetrate into large tumours following systemic administration. It is well known that a magnetic nanoparticle hydrophilic coating (such as PEG or monosialogangliosidecan) can enhance the ability of nanoparticles to evade the RES and, thus, improve circulation time in vivo for up to 6 h after injection. Hydrophilic nanoparticles, such as polyvinylpyrrolidone (PVP) evade the RES nearly 100%. Importantly, though, magnetic nanoparticle based drug delivery systems are not new and have been developed since the 1970s. For example, in 1976, Zimmermann and Pilwat used magnetic erythrocytes for the delivery of a cytotoxic drug, methotrexate. In the 1980s, several authors developed delivery strategies for various drugs using microcapsules and microspheres. The first animal study using magnetic nanoparticle drug delivery was conducted by Lubbe et al., in which small amounts of the Ferro fluid were used as vehicles to concentrate epirubicin locally in tumours. The study concluded that the Ferro fluid did not cause any major abnormalities and there was no LD50. Therefore, the magnetic fluid was termed safe and can be used for cancer treatment. The results led to Phase I and Phase II clinical trials by the same research group in 1996 and 2001. The results demonstrated that magnetic drug targeting with epirubicin was well tolerated by patients and that the nanoparticles were successfully directed to the tumours in about one half of the patients. More recently, several groups reported successful cytotoxic delivery and tumour remission in several animal models including swine, rabbits, and rats.

2.2 Hyperthermia

Hyperthermia is a method of using heat as a treatment for cancer. Fundamentals of hyperthermia are based on the fact that cells (cancer and healthy cells) show signs of apoptosis when heated in the range of 41 ^{0}C to 47 ^{0}Cand necrosis when heated to above 50 ^{0}C. Moreover, tumour cells are considered more susceptible to heat than normal cells due to their higher rates of metabolism which makes hyperthermia a very promising cancer treatment. Hyperthermia can be generated by radio frequency, microwave and laser wavelengths, but magnetic nanoparticle based heating is superior due to the following reasons: (a) it provides a non-invasive way to raise cell temperatures to a therapeutic level; (b) magnetic nanoparticles can be visualized using MRI, thus, combining diagnostic and therapeutic approaches in onetype of particle; and (c) the particles can also be functionalized and combined with other types of treatment such as chemotherapy or radiotherapy. In general, the steps taken for magnetic nanoparticle hyperthermia involve the delivery of particles into tumours and heating of the particles by using alternating magnetic fields to achieve desired temperatures. The heating mechanism of magnetic nanoparticles is based on Brown relaxation (i.e., heat due to friction arising from total particle oscillations) and Ne'el relaxation (i.e., heat due to rotation of the magnetic moment with each field oscillation). It is necessary to note that this heating mechanism is not limited to magnetic nanoparticles but is also applicable for other materials with near infra-red (NIR) absorption capabilities, such as gold nanoparticles or carbon nanotubes. There have been many publications concerning the use of magnetic nanoparticles as hyperthermia agents in vitro and in small animal models. However, a clinical break through was only made in 2007 when Maier-Hauff et al. studied therapeutic hyperthermia induced by heating implanted magnetic nanoparticles. In that study, fourteen patients with recurrent glioblastoma multiform, a type of severe brain cancer, received an intratumoral injection of aminosilane coated iron oxide nanoparticles. The tumour sites were located by several comprehensive MRI scans. The patients were then exposed to an alternating magnetic field to induce particle heating. The superparamagneticiron oxide nanoparticles with core sizes of 15nm were dispersed in water at an iron concentration of 112 mg/ml.

0.1 ml to 0.7 ml of the nanoparticle solution per ml of tumour was injected into each tumour and exposed to a magnetic field of 3.8 to 13.5 k/Am alternating at 100 kHz. The authors demonstrated that all patients tolerated the nanoparticles without any complications. The T90 median temperature was 40.5 ^{0}C and was effectively controlled. Follow-up CT scans and reproducible temperature measurements showed that the nanoparticle deposits were stable for several weeks (Fig. 1).

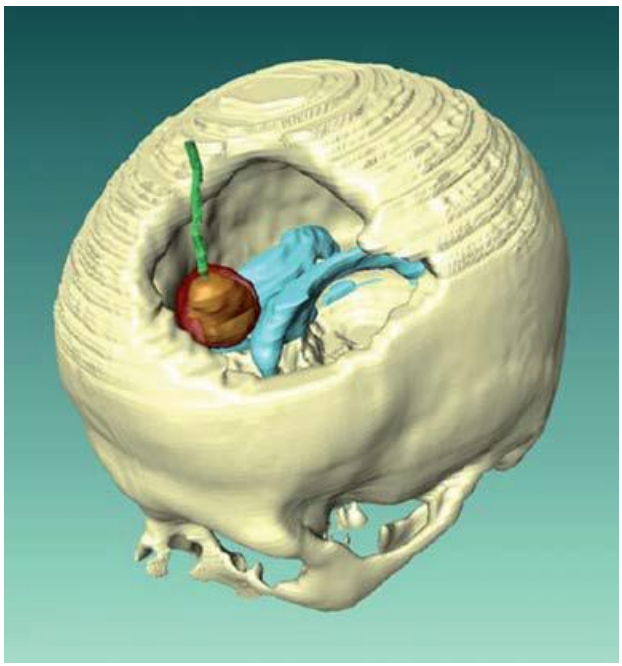

Figure 1: Three-dimensional reconstruction image (MagForce NanoPlan Software) of a skull with a frontal glioblastoma multiform after magnetic resonance imaging and computed tomography. A calculated 42^{0}C treatment isotherm surface (transparentlyred) enclosing the whole tumour (brown), thermometry catheter (green), and ventricle (light blue) are shown.

The same group of researchers also started clinical studies on hyper thermic nanoparticles to treat prostate cancer. They also formed a company, MagForce Nanotechnologies AG, trying to commercialize the iron oxide based magnetic nanoparticles (NanoThermand NanoPlan). A further review concerning the progress of the application of magnetic nanoparticles as hyperthermia agents can be found in.

2.3 Tissue Repair

The new idea of using magnetic nanoparticles for cell therapy originally concerned magnetic labeling to track or monitor cell migration in vivo by MRI. In such cellular therapeutic applications, cells are loaded with magnetic nanoparticles, directed and focused by external magnetic fields to desired sites for tissue repair. Several cell types including erythrocytes, natural killercells and mesenchymal stem cells (MSC) have been used to test this strategy. For example, natural killer cells were magnetically labelled and directed by a magnetic field toward human osteosarcoma cells in vitro to treat bone cancer. Since then, efforts have been made to apply this physical targeting strategy in vivo. Arbab et al. injected magnetically labelled MSCs intravenously through the tail vein of rats and used an external magnetic field to retain cells in the liver. The results showed significantly higher numbers of labelled cells in the animal group exposed to the magnetic field compared to the group without an external magnetic field. A similar method was also used to deliver labelled endothelial cells to the surface of a steel stent. Encouraging results ensued to support the tremendous potentials of cell therapies using magnetic nanoparticles; however, significant efforts are needed especially in targeting and controlling superparamagnetic nanoparticle in the body using an external magnetic field. Despite all of these promising results towards treating cancer and for various cell therapies, the use of iron oxide nanoparticles in orthopaedic applications remains largely unexplored. Due to the positive role iron plays in bone health, Pareta et al. were the first to use magnetic nanoparticles in an effort to reverse osteoporosis. The general idea was to fabricate and modify magnetic nanoparticles with surfactants and drug coatings before injection into porous bone sites. The drug coated magnetic nanoparticles can then be directed through the intricate bone structures by an external magnetic field. Eventually, after the magnetic field is removed, the magnetic nanoparticles can attach to osteoporotic bone, immediately build bone mass while promoting new bone growth.

This idea was further developed by Tran et al. specifically; iron oxides nanoparticles (Fe3O4 and g-Fe2O3) were prepared via wet chemistry methods under high pH. All particles were magnetic with sizes ranging from 10nm to 20nm in diameter. The particles were further tailored with a hydroxyapatite (the main inorganic component of bone) coating to treat osteoporosis.

Bovine serum albumin (BSA) and citric acid (CA) were used as surfactants to prevent magnetic nanoparticle agglomeration. These nanoparticle solutions were later added into osteoblast (bone-forming cells) culture media and incubated with the cells for 1, 3 and 5 days. Osteoblast proliferation tests conducted at 1, 3 and 5 days showed that Fe3O4 coated with hydroxyapatite in the presence of CA and BSA increased cell density compared to the controls. While the mechanism remains unclear, one proposed explanation relates to the adsorption of specificproteins known to promote bone cell functions (such as Vitronectin and fibronectin) on nanoparticle surfaces. Vitronectin is a protein known for promoting osteoblast adhesion, a prerequisite for subsequent cell functions. Previous evidence also demonstrated greater Vitronectin adsorption on nanophase surfaces than on conventional larger size micron surfaces. Therefore, fabricating nanoparticles that do not agglomerate and promote Vitronectin adsorption might be essential for promoting osteoblast functions. Clearly, this study exhibited greater potential in treating not only osteoporosis but also other local bone diseases and fractures. However, further evidence is needed to confirm enhanced osteoblast functions in the presence of iron oxide nanoparticles and in vivo verification of such promising in vitro results.

2.4 Infection

Fighting against bacterial infection has always been crucial incany biomedical application. It has been known for quite a while that bacteria can adhere to solid surfaces of almost any biomedical instrument, catheter, and implant, creating biofilms leading to many infectious diseases. As an indication of our failed attempts so far, an increasing number of bacteria have built resistance to conventional antibiotics (such as ampicillin, ciprofloxacin, cloxacillin, methicillin, and penicillin).

Many believe that using magnetic nanoparticles to carry antibacterial agents (TiO2, ZnO, MgO, chitosan, copper, silver, etc.) can provide an alternative treatment method for bacterial infections. For example, Lee et al. synthesized magnetic beads coated with silver (Ag) to inhibit Escherichia coli (E. coli) colonization. These microspheres were localized by an external magnetic field showing clear antibacterial activity in the focused zone (Fig. 2).

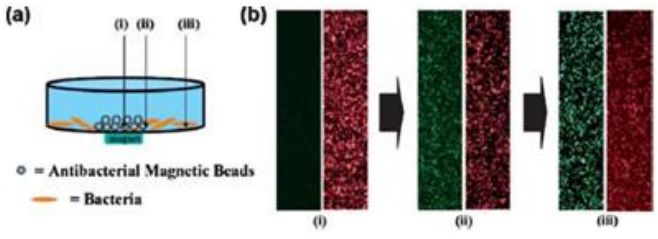

Figure 2: Localized delivery of multilayer coated magnetic micro particles by magnetic fields: (a) scheme of the experimental setup and (b) fluorescence microscope images at locations (i), (ii), and (iii) in the Petri dish. Live and dead E. coli were stained with green and red fluorescence dyes, respectively. The distances from (i) to (ii) and (iii) were approximately 3 and 15 mm, respectively. The width of each image is 60 mm.

By reducing the magnetic particle size to the Nano-scale, it is expected that the consequent with higher surface – volume ratios, larger amounts of antimicrobial drugs can be loaded and, thus, provide a more effective treatment.

3. Challenges

3.1 Toxicity of nanoparticles

Recent developments in nanotechnology have allowed for the fabrication of a wide range of Nano-scale materials. It has been reported that over 500 consumer products contain nanoscience and nanotechnology related materials. Currently, there are at least 12 nanomedicines already approved by the FDA and many more are in their final development stages. Clearly, the toxicity of magnetic nanoparticles is one of the most important issues that needs further investigation. It has been difficult to report accurate nanoparticle toxicity since toxicity depends on numerous factors including dose, chemical composition, method of administration, size, biodegradability, solubility, pharmacokinetics, bio distribution, surface chemistry, shape and structure, to name but a few.1 Among these factors, modification of magnetic nanoparticle surface properties can be a main tool to reduce toxicity. To fully understand the toxicity of nanoparticles, extensive cytotoxicity studies should be conducted not only in vitro but also in vivo since the in vitro experimental results can be misleading. Importantly, it has been reported that some nanomaterials interfere with cell viability assays. For example, Monteiro-Riviere et al. recently demonstrated that classical dye based assays (such as MTT and neutral red (NR) assays that determine cell viability) produce invalid results with some nanomaterials due to nanoparticle/dye interactions. Therefore, several different assays would be necessary to confirm the toxicity of nanoparticles. Regarding the toxicity of magnetic nanoparticles, the most widely studied nanoparticles are iron oxide nanoparticles. These nanoparticles (such as Feridex_, Endorem_, etc.) have been widely used in MRI applications and are considered biocompatible. Cengelli et al. reported that iron oxide nanoparticles coated with dextran and various PVAs were not cytotoxic to brain-derived endothelial EC219 cells and murine N9 and N11 microglial cells. M€uller et al. demonstrated that the iron oxide nanoparticle Ferumoxtran-10 (Sinerem_, Guerbet, France Combidex_, Advanced Magnetics, USA) had no toxic effects for human monocyte-macrophage interactions at concentrations up to 1 mg/ml over 72h and may be only slightly toxic at the extremely high concentrations of 10 mg/ml.

3.2 Targeting and controlling magnetic nanoparticles by an external magnetic field

One of the largest challenges in magnetic particle based therapeutics is the ability to direct the magnetic nanoparticle drug carriers to the desired site for treatment. Many efforts have been employed to develop magnetic carriers; however, control systems for these nanoparticles are still very simple, mostly consisting of just a permanent magnet placed near the target site.

Using this control system is not ideal for particle focusing, and moreover, the magnetic field from permanent magnets can only penetrate into a tissue depth of 8–12 cm, thus, this strategy cannot be applied for deeper tumours. One way to enhance local drug delivery is by using magnetic implants which can attract magnetic nanoparticles if needed. Shapiro also suggested using dynamically controlled magnetic fields to focus magnetic carriers to deep tissue targets. A magnetic control model consisting of 8 magnets was also developed where each magnet was controlled independently using a special algorithm. The modelling results demonstrated that dynamically controlled magnets could drive a magnetic fluid through the centre and created a hot spot at the target (Fig. 3).

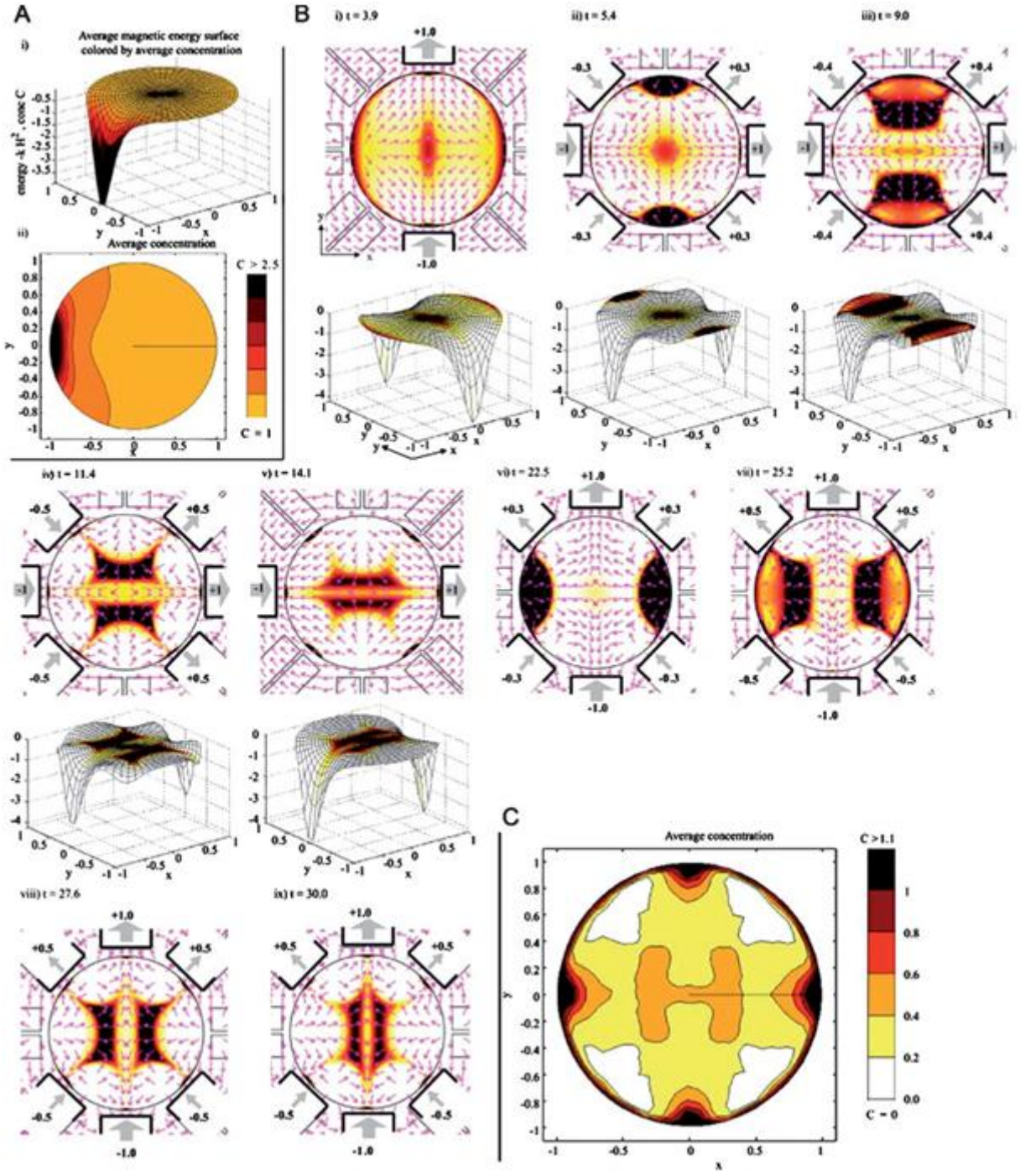

Figure 3: Modeling results of a dynamic control magnet system. (A): Constant actuation by a single magnet on the far left; (B): Dynamic control was achieved by turning a magnet on and off to drive the ferrofluid toward the center; and (C): A time-averaged ferrofluid concentration map showing the hot spot at the center.

Although this method seemed very promising, it is necessary to note that controlling nanoparticles in vivo is significantly more complicated. There are some available models regarding this matter, but an optimized algorithm incorporating complex vasculature geometry and blood flow still needs to be developed.

4. Commercialization and Conclusion

In summary, there is continual exciting evidence that strengthen the belief that nanometre particles can improve disease prevention, diagnosis, and treatment; especially new studies highlighting the role magnetic nanoparticles may play in reducing infection and promoting tissue growth. The future of magnetic nanoparticle applications involves the creation of multifunctional therapeutic materials and the ability to target those nanoparticles to desirable sites. Many products based on magnetic nanoparticles are in their final development stages with several already on the market .With new knowledge gained concerning how the human body interacts with magnetic nanoparticles (from killing cancer cells to healing tissues to reducing infection), advanced applications of magnetic nanoparticles for treating a wide range of diseases may be available in the very near future.

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