Review article

The application of magnetic nanoparticles in the treatment and monitoring of cancer and infectious diseases

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Magnetic nanoparticles (MNPs) have shown promise in a number of biomedical applications, including: magnetic hyperthermia, enhancing magnetic resonance imaging (MRI) data, supplementing tissue engineering efforts and improving the delivery of drugs to difficult to reach microniches. Their inclusion in the treatment pathways of various pathologies highlights a growing trend towards the integration of novel biotechnologies in healthcare and therapeutic settings. Superparamagnetic nanoparticles (SPNs) allow clinicians to produce a localized thermo-ablative effect leading to the destruction of bacterial biofilms and cancer cells. In addition, through the physical disruption of bacterial membranes, SPNs can sensitize resistant bacterial cells to antibacterial compounds. MNPs have also improved the delivery of bactericidal compounds to restricted microniches, and could, therefore, potentially be used in the treatment of conditions that require therapeutic interventions to cross the blood–brain barrier. Furthermore, MNPs have been investigated as novel MRI contrast agents due to their unique combination of favourable magnetic properties, biodegradability, and surface functionality.

Key words: magnetic nanoparticles, hyperthermia, magnetic resonance imaging, superparamagnetism, cancer, infectious disease

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Introduction

There is increasing interest in the use of magnetic nanoparticles (MNPs) for a range of biomedical applications including the diagnosis and treatment of cancer and infectious diseases alongside enhancing tissue engineering techniques (Cho, Oh and Oh, 2010; Banobre-Lopez, Teijeiro and Rivas, 2013; Sadhukha, Wiedmann and Panyam, 2013; Singh, Barick and Bahadur, 2015). Characterized by their nano-dimensions, MNPs have been successfully conjugated to chemotherapeutic agents and the fragment antigen-binding domains of antibodies to aid MNP targeting and therapeutic effect (Brasseur, Couvreur and Kante, 1980; Jiao et al., 1996; Jordan et al., 1999; Mandal, Fleming and Walt, 2002; Qiao et al., 2012; Quarta et al., 2015). Furthermore, MNPs exhibit magnetic properties and, therefore, obey Coulomb’s law of electrostatic force interaction; these properties allow the particles to be manipulated using magnetic field gradients. MNPs respond to alternating current magnetic fields producing an energy transfer effect characterized by magnetic hysteresis producing a localized thermo-ablative effect (hyperthermia) leading to cellular death in cancerous and bacterial cells (Huang and Hainfeld, 2013).
Magnetism

Magnetism arises from two sources: electrical currents and the magnetic spin moments of elementary sub-atomic particles, such as electrons (Kiyama et al., 1996; Sugiyama et al., 2002). In most cases, the electrons that compose materials are arranged such that their individual magnetic spin moments cancel each other out and therefore produce no overall magnetizability. However, in some cases, the individual magnetic spin moments of elementary sub-atomic particles can spontaneously align and produce an overall magnetizable of the entire, or part of, the material. Different materials exhibit different types of magnetism, such as paramagnetism and ferromagnetism. Paramagnetism is observed in materials with an unpaired electron and is characterized by the formation of internal-induced magnetic domains in the same direction of an applied magnetic field; thus, paramagnetic materials are attracted to external magnetic field gradients (Stevens, 1967).

In ferromagnetism, the overall magnetizable of a ferromagnet can spontaneously separate into smaller regions (magnetic domains) if the diameter of the material is larger than a critical value, \( D_C \). Ferromagnetic materials are also subject to the Curie temperature (\( T_C \)). \( T_C \) is different for each material (Table 1) and dictates the temperature at which permanent magnetizable can be substituted by induced magnetism.

Superparamagnetism arises in single-domain ferromagnetic and ferrimagnetic materials when the diameter of the magnetic material is below a critical value (\( D_C \)), typically between 3 and 50 nm (Bean and Livingston, 1959). \( D_C \) is dependent on the material, as demonstrated by Table 1. In this case, the magnetizable of the material arises from a singular giant magnetic moment; this magnetic moment represents the sum of each magnetic spin moment produced by each subatomic particle within the material. The resulting magnetic moment principally has two stable orientations that are antiparallel to each other; these two stable orientations are separated by an energy barrier. In specific conditions, thermal fluctuations can induce a transition between the two orientations and, in doing so; reverse the polarity of the material (Fannin and Charles, 1994). The mean time for the completion of this transition is termed the Néel relaxation time (\( T_N \)). \( T_N \) can represent a few nanoseconds or a number of years and is defined by the Néel-Arrhenius equation. In determining whether a material is superparamagnetic, consider the observation and measurement of single-domain nanoparticle over a specified time, \( T_M \). If \( T_N \) for a MNP is longer than \( T_M \), the magnetic particle is considered to exist in a blocked magnetic state. In contrast, if \( T_N \) is shorter than \( T_M \), the nanoparticle is considered superparamagnetic. In short, the determination of a nanoparticle as either blocked or superparamagnetic depends on measurement time. Superparamagnetic materials exhibit similar properties to paramagnets; however, they have a higher magnetic susceptibility rendering them highly sensitive to externally applied magnetic fields and minimal remanence ensuring that the magnetic particle is only magnetized in the presence of an externally applied magnetic field (Kneller and Luborsky, 1963; Schenc, 1996). These characteristics make superparamagnetic materials popular choices when considering the functionalisation of nanoparticles in healthcare and therapeutic settings.

MNPs are composed of a metallic core stabilized and functionalised by the addition of an outer shell with conjugated functional groups. MNPs are normally smaller than 100 nm and can be synthesized from any material characterized by some degree of magnetism (Gupta and Curtis, 2004; Liu et al., 2004; Maity et al., 2009). In most cases, the metallic core is composed of iron or iron-oxide-based compounds, such as maghemite (\( \gamma -Fe_2O_3 \)) or magnetite (\( Fe_3O_4 \)). It is principally the presence of the magnetic core that ensures the MNP can be manipulated using magnetic field gradients. MNPs are more stable and responsive as single-domain structures deployed in conditions that exceed the Curie temperature and are therefore superparamagnetic. Superparamagnetic nanoparticles (SPNs) exhibit many desirable characteristics, such as low remanence and coercivity, coupled with a high magnetic susceptibility (Bean and Livingston, 1959; Kneller and Luborsky, 1963). These features, along with a reduced risk of agglutination (at room temperature) make SPNs attractive

Table 1. Physical and chemical properties of six compounds often used to produce MNPs. Data taken from multiple sources, including: Tang, Sorensen, Klabunde and Hadjipanayis (1991) and Demortière et al. (2011) for iron and iron-oxide values; Sivakumar et al. (2016) for strontium ferrite values; Connelly, Loomis and Mapother (1971) for nickel values; Gupta, Li and Xiao (2000) for chromium oxide values; and, Morris and Cason (1968) for europium oxide values.

| Material                  | Chemical symbol | Magnetism       | Curie temperature (K) | \( D_C \) (nm) |
|---------------------------|-----------------|-----------------|-----------------------|----------------|
| Iron                      | Fe              | Ferromagnetic   | 1043                  | ~15            |
| \( \gamma \)-Iron (III) oxide | \( \gamma -Fe_2O_3 \) | Superparamagnetic | 948                  | <100           |
| Strontium ferrite         | SrFe\(_{12}\)O\(_{19}\) | Superparamagnetic | ~450                  | <100           |
| Nickel                    | Ni              | Ferromagnetic   | 627                   | 55             |
| Chromium (IV) oxide       | CrO\(_2\)       | Ferromagnetic   | ~390                  | <100           |
| Europium oxide           | EuO             | Paramagnetic   | 69                    | <100           |
candidates in a range of biomedical applications. MNPs, especially in healthcare applications, must remain stable over long periods of time in chemically and physically challenging microenvironments such as hypoxic tumour conditions. Unfortunately, SPNs often tend towards instability and degradation into their constituent elements; this is especially true in the case of naked metallic nanoparticles which are often easily oxidized and thus lose their magnetism in oxygen-rich environments (Lévy et al., 2010).

Finite-size and surface effects

In addition to the propensity for SPNs to become unstable with time, finite-size and surface effects also impact the magnetic character and magnetizability of MNPs (Issa et al., 2013). The single-domain limit ($D_C$) and superparamagnetic limit ($T_N$) are the two most studied finite-size effects. Both $D_C$ and $T_N$ have been discussed in previous sections; therefore, this section will focus on exploring the impact of surface effects. Surface effects refer to the relationship between nanoparticle size and the probability of an internal atom interacting with the outside environment; specifically, as the size of MNPs decrease, there is a higher probability that atoms contained within the nanoparticle will become surface atoms and with a higher percentage of surface atoms, surface effects become even more important (Batlle and Labarta, 2002). Surface effects, for example the creation of a magnetoically null layer on the MNP surface, can lead to an overall decrease in magnetizable, especially in iron oxide-based MNPs (Nunes and Yang, 1998). Interestingly, it should be noted that while iron oxide-based nanoparticles record a decrease in magnetism with reduced size as a result of surface effects, smaller metallic MNPs, such as those based on a cobalt core, have recorded an increase in magnetism with decreasing size (Respaud et al., 1998).

Encapsulation and protection strategies

SPN instability and the potent cytotoxicity of some magnetic materials mean it is important to develop masking strategies which stabilize MNPs against degradation and improve biocompatibility (Karlsson et al., 2008). Protection strategies often involve the addition of either an organic layer, such as polymer poly-(methyl methacrylate) or inorganic layer, such as silica, to coat the metallic core (Jiao et al., 1996; Mandal, Fleming and Walt, 2002). Surface coatings ensure that MNPs do not agglomerate while shielding the magnetic core from reactive species in the external environment. They also confer additional functionality upon the MNP, for example, particles can be coated with targeting ligands or antibodies that target specific cells (Sung et al., 2013). Polymer-based shells, such as PEG and dextran, are often used where there is an increased risk of opsonisation; principally due to the size of the nanoparticle exceeding 100 nm and therefore more vulnerable to sequestration by the reticuloendothelial system (Yadav et al., 2011; Wu et al., 2015). However, while PEG-based shells reduce the risk of MNP opsonisation, their neutral pH prohibit the conjugation of functional groups; as a result, synthetic polymers such as poly(acrylic acid) are preferred for their ability to carry and bind to biological macromolecules, such as DNA (Wan et al., 2013). Interestingly, in some cases, using a less reactive metallic shell improve nanoparticle stability and bio-compatibility through combining two otherwise different magnetic phases boosting the overall magnetic properties of the structure via the exchange-bias effect (Zheng et al., 2004; Khurshid et al., 2014). The exchange-bias effect is caused by the quantum mechanical pairing of two magnetic atoms across the interface between a ferromagnetic and anti-ferromagnetic material (Stamps, 2001). Exchange coupling has been demonstrated in a number of systems (including; Fe3O4-CoO) and can provide a further source of anisotropy helping to stabilize unreliable nanocomposites (Zeng et al., 2002). Altogether, these protection strategies work to ensure the longevity of MNPs in biomedical applications.

Figure 1. Functionalisation and therapeutic applications of MNPs. MNPs consist of a magnetic core stabilized by the addition of a protective biocompatible coating. The addition of functional groups (e.g. targeting ligands, fluorophores, therapeutic drugs etc.) to the outer MNP coating are often used to enhance medical imaging techniques, improve molecular targeting and allow theranostic-based therapies.

Therapeutic uses of MNPs

MNPs have a range of uses including: enhancing the signal obtained from magnetic resonance imaging (MRI) techniques, promoting the accumulation and deposition of biotherapeutic compounds such as genes and peptides in rewarding micro niches, and mediating the destruction of cancer cells and biofilms through the production of a local thermo-ablative effect,
often referred to as magnetic hyperthermia. An overview of the therapeutic applications of MNPs is shown in Fig. 1.

### Magnetic resonance imaging

MRI is often used in the diagnosis of cancer and other pathologies (Moore et al., 2013; Schoots et al., 2015). Unlike other imaging modalities, MRI does not require the use of ionising radiation to image tissues but rather uses the magnetic character of protons for image creation. Under normal conditions, protons are randomly orientated producing no overall magnetic moment. Once the MRI apparatus has produced the primary magnetic field, protons either align themselves parallel or anti-parallel to the primary magnetic field. This process, referred to as longitudinal magnetizable, produces a net magnetic vector (M) in the direction of the primary magnetic field. Gradient coils embedded within the primary magnets alter the primary magnetic field allowing MRI to image directionally in the x, y, or z axes. Protons precess the long axis of primary magnetic field in-phase and out of phase at a rate directly proportional to the magnetic field strength (Schick et al., 1991). Clinicians then use radio frequency pulses to force protons into a high-energy, in-phase state; thus, the net magnetizable vector turns 90° towards the transverse plane. Ultimately, protons relax to their normal state via spin-lattice (T1) and spin-spin (T2) relaxation as protons transition back to their original longitudinal out of phase state (Houmard, Smith and Jendrasiak, 1995; Hsu and Lowe, 2004). In reality, protons de-phase much quicker than T2 because of inhomogeneities in the magnetic field; the combination of T2 relaxation and these inhomogeneities is termed T2* (Kamada et al., 1994). It is the relaxation of protons from the transverse plane to the longitudinal plane that produces fluctuations in the net magnetic vector and is then used to image tissues.

### Contrast agents

Contrast agents are used to enhance the quality of MRI images and are classified based on their ability to impact T1 or T2/T2* relaxation times (Kato et al., 2003; Xing et al., 2008). T1 contrast agents alter the longitudinal (T1) relaxation times of water protons to produce bright positive signal intensity in images and increase the conspicuousness of cells. T2/T2* agents alter the transverse (T2/T2*) relaxation times of water protons producing dark negative signal intensities in images. SPN-based contrast agents principally impact T2* relaxation, allowing regions to be identified as hypo-intense signals on the obtained image, although SPN-based contrast agents are also known to impact T1 (Qin et al., 2007). Given that the ability for SPNs to impact T2 and T2* relaxation time is proportional to their ability to disrupt the local magnetic field; SPN-based contrast agents with high magnetic susceptibility and relaxivity are preferred. In addition to imaging tissues and cell clusters, SPNs have been used to label and subsequently track individual cells (Nitin et al., 2004). Several non-specific SPN-based contrast agents are available for general imaging purposes (Tan et al., 2010); however, these non-specific SPNs are unable to efficiently accumulate in restrictive microniches, such as tumour sites. Targeted delivery of SPNs, using tumour-specific targeting moieties attached to the SPN outer shell, can facilitate their accumulation in cancer sites improving MRI resolution; for example, conjugation of anti-α-fetoprotein and anti-glypican antibodies to the SPN shell can be used to selectively target hepatocellular carcinoma (Li, 2015). Unfortunately, only a small number of SPN-based specific contrast agents have been produced to-date, principally due to the lack of highly specific biomarkers (Bakhtiary et al., 2016). Nevertheless, non-specific SPN-based contrast agents have arguably revolutionized tissue imaging and diagnostics; future research into targeted contrast agents will augment the availability of MRI as a non-invasive and robust system for imaging specific pathologies.

### Magnetic hyperthermia

Magnetic hyperthermia is a term used to describe the generation of heat by MNPs in response to the application of an external alternating magnetic field. Cycles of magnetizable lead to the loss of thermal energy to the environment driven by hysteresis losses in multi-domain MNPs, Néel or Brown relaxation, and frictional losses due to the dynamics of viscous suspensions. In multi-domain ferromagnetic or ferrimagnetic materials, the production of heat primarily occurs through hysteresis losses, as demonstrated by the presented hysteresis loop. Integrating the area of the hysteresis loop quantifies the amount of thermal energy lost to the environment (Carrey, Mehdou and Respaul, 2011). Hysteresis losses are largely dependent on the strength of the applied magnetic field. The size and the nature of a MNP domain structure also have a profound influence on the hysteresis of the MNPs, and, consequently, on their hyperthermia properties (Hergt et al., 2008). Superparamagnetic materials contribute to magnetic hyperthermia, despite (under normal conditions) not being characterized by hysteresis, due to Néel and Brownian relaxation. In this case, the magnetizable of SPNs can lag behind the actual magnetizable of the applied magnetic field thus producing a hysteresis loop conferring hyperthermia properties upon superparamagnetic materials (Usov and Grebeshchikov, 2009). SPN magnetizable lags behind the actual magnetizable of the applied magnetic field because the magnetizable of nanoparticles in a fluid is not stable and decays with a characteristic relaxation time. Initially, when a magnetic field is applied, nanoparticles align with or against the applied magnetic field. The delay between the magnetic field reversal and the one of magnetizable is called Brownian relaxation, as previously described. In this context, Brownian relaxation generates heat through friction between MNPs and their surrounding medium, for example, blood. Brownian relaxation is considered to be size and viscosity dependent because as MNPs increase in size and the viscosity of the carrier fluid increases, Brownian relaxation time also increases (Kötitz, Fanin and Trahms, 1995). The Néel and Brownian relaxation time values are important because the heating effect depends on the energy delivered per
second. Clinicians can only re-magnetize MNPs only after they have relaxed and are, therefore, susceptible to magnetizable again. Therefore, the alternating magnetic field frequency must be matched to the calculated relaxation times for an efficient heating effect to be produced. Magnetic hyperthermia is one of the many possible applications of MNPs in the treatment of cancer and infectious diseases.

**Magnetic hyperthermia in cancer therapy**

Tumour vasculature has been shown to possess distinctive anatomical and biochemical characteristics arising from a lack of adequate perfusion leading to the generation of hypoxia and acidosis rendering cancerous cells thermally sensitive (Bailie, Winslet and Bradley, 1995; Fenton et al., 1999). Tumour growth can be halted by heating cells to 40°C for 30 min or more; however, it is difficult to raise whole body temperature without also promoting adverse biochemical side effects. In 2010, Balivada et al. demonstrated the production of a localized thermo-ablative effect that did not induce systemic hyperthermia in vivo. Here, the researchers reported an increase of 11°C–12°C in C57BL/6 mice mediated by the accumulation and subsequent activation of MNPs. In addition, Balivada et al. (2010) demonstrated that as the iron concentration of the magnetic nanocomposites increased from 5 μg/ml to 25 μg/ml, the number of viable tumour cells decreased from approximately 480,000 to 150,000 indicating the increase in iron concentration had an in vivo cytolytic action.

Other studies have demonstrated the effectiveness of magnetic hyperthermia as a prospective therapeutic target (Yanase et al., 1998a, 1998b; Jordan et al., 2006; Balivada et al., 2010). Initial work by Yanase et al. (1998b) used magnetite-based cationic liposomes in the in vivo treatment of brain gliomas in F344 rats. Here, the researchers found that the average tumour volume decreased from 30,377 to 2,684 mm³ with three rounds of treatment. Interestingly, one case from the test group did not appear to respond to treatment as a result of abnormal tumour morphology that had metastasized. This particular case seems to suggest that the application of magnetic hyperthermia in the treatment of multi-site and metastatic cancers may be more technically demanding (Yanase et al., 1998b).

Building on this, Jordan et al. (2006) used dextran-coated MNPs in the in vivo treatment of malignant glioblastomas in Fisher rats. Similar to Yanase et al. (1998), the researchers found that there was a statistically significant difference (p < 0.01) in the mean survival between control and therapy groups. Overall, an increase in intra-tumoural temperature from 43°C to 47°C precipitated an increase in mean survival of the animal from 15.4(±6.3) to 39.7(±3.5) days, representing a 4.5-fold increase in survivability. Separately, Balivada et al. (2010) used iron and iron oxide-based MNPs in the in vivo treatment of melanoma in C57/BL6 mice. Here, the researchers found a statistically significant (p < 0.1) decrease in overall tumour weight from 1.6 (control) to 0.75 mg following MNP therapy. These studies appear to show that magnetic hyperthermia can reduce the viability of certain cancer cell lines, however, it is unable to entirely eradicate tumours.

**Treatment with MNPs with secondary interventions**

MNPs have a clear tumoricidal potential, demonstrated by a reduction in tumour mass in many studies, but complete regression remains elusive. Coupling magnetic hyperthermia with classical therapeutic interventions possibly represents the best opportunity to tackle difficult clinical cases (Yanase et al., 1998a; Ito et al., 2003). In this light, Yanase et al. (1998a) coupled magnetic hyperthermia with immunotherapy to induce the activation and mobilization of tumouridal (CD3⁺, CD4⁺, CD8⁺ and natural killer) cells against gliomas in Fisher (F344) rats in vivo. Here, the researchers reported MNPs were able to induce a host immune response against tumour cells alongside producing a localized thermo-ablative effect leading to partial and in some cases, complete tumour regression. Moreover, Ito et al. (2003) demonstrated that using MNPs in conjunction with a course of immunotherapy (injection of interleukin-2, IL-2 or granulocyte macrophage-colony stimulating factor, GM-CSF) notable regression of melanoma tumours in mice could be achieved in vivo (75% and 40% success using IL-2 and GM-CSF, respectively). This research highlights that the combined usage of magnetic hyperthermia and classical treatments, such as immunotherapy, can be used in conjunction in the treatment of cancer.

**Routes of MNP administration**

There are many cases where the intra-tumoural or intra-venous application of MNPs would decrease the efficacy of magnetic hyperthermia and also require invasive surgery, such as the treatment of bronchiolar and alveolar lung cancer (Patton, Fishburn and Weers, 2004). Despite the perfuse nature of the lung, intra-venous delivery of therapeutic compounds often leads to a broad, non-specific distribution of agents. In addition, alveolar macrophages are known to effect the clearance of particulates from the lung into the systemic circulation; therefore, alternative routes for the administration of MNP-based treatments must be developed. One such example comes from Sadhukha, Wiedmann and Panyam (2013) who demonstrated the use of inhalable iron oxide-based MNPs in the treatment of non-small cell lung cancer. Using epidermal growth factor receptor functionalised MNPs they targeted lung tumour cells in mouse orthotopic models in vivo. Here, functionalization of the MNPs through the addition of targeting matrices resulted in a 4.5-fold higher cellular uptake than the untargeted control leading to a lower final lung weight (p < 0.05). Additional research by Stocke et al. (2015) led to the production of microparticles composed of iron oxide-based MNPs and D-mannitol for delivery by aerosol; aerosol performance studies and heating studies carried out on human lung A549 cells demonstrated these microparticles have a moderate in vitro cytotoxicity. Together, these inhalable nanocomposites represent a novel route for the administration of MNPs for magnetic hyperthermia treatment of the lungs.
Human trials of MNPs

Initial trials into the applicability of magnetic hyperthermia in humans have reported largely positive results. In 2007, Maier-Hauff et al. showed that MNPs were capable of generating the required intra-tumoural temperatures (42.4°C–49.5°C) in order to treat unhealthy tissue in humans in vivo. Further research by Maier-Hauff et al. (2011) determined that MNPs could be safely used in the in vivo treatment of patients suffering with recurrent glioblastoma multiforme. In this case, the researchers reported an extended median first tumour recurrence from the 6.2 to 13.4 months (observed in the reference study); they were also able to extend the median primary tumour diagnosis point from 14.6 to 23.2 months (Stupp et al., 2005). These results demonstrate that magnetic hyperthermia is a safe and viable option for inclusion in the clinical repertoire for tackling single-site and metastatic cancers.

Magnetic hyperthermia in the treatment of infectious diseases

Magnetic hyperthermia has emerged as a promising technique for the treatment and control of infectious diseases. Given that hyperthermia leads to the physical destruction of pathogenic organisms, efficacy is expected to be independent of the drug-resistance status of the pathogen. Studies by Park et al. (2011) showed that iron oxide-based MNPs could be used to inactivate bacterial biofilms in vitro. Furthermore, they demonstrated that magnetic hyperthermia (using 20–60 mg/ml SPN solutions) is capable of severely disrupting the membrane integrity of Pseudomonas aeruginosa PA01 biofilms in vitro. Thus, even if treatment by magnetic hyperthermia fails to completely destroy the target biofilm, through disrupting the cell wall it may render drug-resistant bacteria susceptible to bactercidal compounds. Similarly, O’Toole, Ricker and Nixoll (2015) cultured P. aeruginosa biofilms and then subjected them to thermal shocks (between 50°C and 80°C) in vitro. They reported that with an increase in temperature from 37°C to 80°C the average log (colony-forming units cm⁻²) decreased from 8.68 (+0.38) to 2.58 (+0.61). Altogether, these results demonstrate that magnetic hyperthermia is a viable alternative mechanism, with albeit limited application in therapeutic settings if temperatures as high as 80°C are required, for tackling the proliferation of bacterial biofilms and bacterial infections. More recently, Singh, Barick and Bahadur (2015) examined the efficiency of magnetic hyperthermia in reducing the viability of Escherichia coli colonies in vitro. Using iron-based MNPs, they demonstrated magnetic hyperthermia could reduce cell viability by up to 99.97%. These results are broadly commensurate with prior research conducted by Thomas et al. (2009) who found iron-based MNPs stabilized using tiopronin, could reduce the number of viable colonies of Staphylococcus aureus by a magnitude of 10⁷, following 4 min of magnetic hyperthermia treatment in vitro. Interestingly, Singh, Barick and Bahadur (2015) also showed that magnetite and magnetite-zinc oxide MNPs have an intrinsic bactercidal effect. In this light, it is reasonable to conclude that magnetic hyperthermia may become one of the many tools used in the treatment of infectious diseases.

MNP...
(Nawwab Al-Deen et al., 2011); for example, nanoparticles conjugated to a nucleic acid–based vaccine that encoded for the *Plasmodium yoelii* merozoite surface protein (MSP19) were able to transfect African green monkey kidney cells at a higher rate than comparable chemical-based methods in vitro. In later studies Nawwab Al-Deen et al. (2014) used an improved experimental design to enhance the transfection of *P. yoelii* merozoite MSP19 and maturation of dendritic cells with similar success to their previous study. Given the MSP19 protein can confer resistance to malaria these results demonstrate the potential for MNPs to contribute to the prevention of infectious diseases as well as their treatment.

Moreover, SPNs have been used to mediate the delivery of therapeutic proteins promoting their deposition at target sites (Veiseh et al., 2009; Kim et al., 2010; Niemirowicz et al., 2015). Cathelicidin LL-37 (CLL-37) and chlorotoxin (from *Leiurus quinquestriatus*) are two peptides both known to bind to and inhibit the proliferation of cancer cells (Ojeda, Wang and Craik, 2016). In 2015, Niemirowicz et al. attached CLL-37 to MNPs and observed a decrease in colon cancer cell (DLD-1 and HT-29 cells) viability coupled with an increase in apoptosis compared to treatment with free CLL-37 in vitro. Chlorotoxin-coated SPNs have been shown to inhibit the proliferation of glioma cells up to 98% compared to free chlorotoxin which was shown to inhibit cellular proliferation by only 48% in vitro (Veiseh et al., 2009). These results indicate that the delivery of therapeutic peptides might be significantly improved using a magnetically driven approach.

Cell-based therapies

Stem cell and immune cell-based therapies have long been investigated as treatments for various life-threatening conditions, such as ischaemia (Cores, Caranasos and Cheng, 2015). However, poor cell retention often hinders cell transplantation efforts. In response, MNPs have been conjugated to the surface of stem cells and immune cells to improve graft retention and subsequent gene transfection. In one such example Kyrtatos et al. (2009) demonstrated the successful delivery of human CD133⁺ endothelial progenitor cells to sites of vascular injury to male Sprague–Dawley rats (carotid artery injury models) in vivo. Through the application of an external magnetic field accumulating MNPs at sites of catheterization, the researchers demonstrated a 5.4-fold increase in CD133⁺ cell engraftment, reduced restenosis, and fewer incidences of scar tissue formation leading to a re-obstruction of the blood vessel. More recently, Cheng et al. (2012) demonstrated the therapeutic potential of nanoparticle-labelled cardiospheres in vivo. Here, they injected nanoparticle-labelled cardiospheres injected into the left ventricular cavity of female Wistar Kyoto rats leading to 4-fold higher cell retention in both the short-term (24-h period) and long-term (3 week period). It is also possible, in addition to functionalising the cell membranes of immune cells with SPNs, to stimulate the endocytosis of MNPs by cells of interest allowing the host cell to then exhibit superparamagnetic properties demonstrating an example of molecular mimesis (Riemer et al., 2004).

## Conclusion

In the past decade MNPs, specifically SPNs, have proved a useful tool in promoting the deposition of therapeutic compounds; mediating the destruction of cancer cells and biofilms; and, improving the sensitivity of MRI techniques. Production of specialized encapsulation strategies has shown that MNPs can now be targeted to specific tissues, including cancer cells, revealing the possibility for a novel personalized approach to MNP-mediated treatment. Similarly, developments in the field of magnetic hyperthermia have mediated near complete tumour regression and the re-sensitization of drug-resistant bacterial strains to antibiotics. These features characterize MNPs as versatile and adaptable tools for use in a broad range of biomedical contexts. There are still limitations to the use of MNPs in the diagnosis and treatment of cancer and infectious diseases, however, progress in this field is evident and it is likely the use of MNPs will become a staple component in the treatment of both infectious diseases and cancer in the future.

## Author biography

I graduated with a degree in Biomedical Science from Keele University in 2016 and have a keen interest in biotechnology and their applications to healthcare dilemmas. I am currently a doctoral student at Keele University looking at the molecular mechanisms by which molecules of the innate immune system recognize and bind to their natural targets and effect their clearance through interaction with components of immune system pathways.

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