Applications of Magnetic Nanoparticles in Cancer Therapy

Emily Erstine
University Physics II Honors Project
April 20, 2009

Introduction

According to scientific research collected by the American Cancer Society, cancer claims the lives of over 1500 Americans daily and over 565,000 annually [3]. Cancer is responsible for one in four deaths in the Unites States and is the second foremost cause of death only behind cardiovascular disease [3]. Based on estimates for 2008, it is likely that over 2.5 million new cancer cases present each year [3]. Many of these newly diagnosed patients will undergo routine treatment programs of radiation and/or chemotherapy.

Radiation and chemotherapy are systemically toxic to patients, damaging not only neoplastic tissue, but all vital tissue in the body, which causes severe side effects. Such side effects include cardiac, renal, hepatic, etc. toxicities, leading to a miserable existence for the patient, considerably reducing quality of life for the treatment duration and perhaps chronically if the toxic effects are irrevocable. The prospect of localizing cancer treatment with the objective to lessen or eliminate severe systemic side effects dates back to 1957 in Gilchrist and associates' pioneering biomedical research of employing superparamagnetic nanoparticle hyperthermia to treat cancer tumors [12, 5, 33, 37]. The results of the Gilcrest investigations lead to an ever-expanding field in biomedical research that is still considered cutting-edge today.

This biomedical research includes multi-faceted techniques of employing magnetic nanoparticles as contrast agents for diagnostic and post-treatment magnetic resonance imaging (MRI); site-specific delivery systems of drugs, immunostimulants, radionuclides, and genes; as well as agents for localized hyperthermic treatment. The potential applications of magnetic nanoparticles in cancer therapy are intimately related to the nanoparticle systems' structures and functions. This paper explores basic structures and functions of magnetic nanoparticle therapy systems and their potential biomedical applications in localized cancer treatments as suggested from experimental evidence.

Structures of Magnetic Nanoparticles for Cancer Therapy

The structures of magnetic submicronic colloidal [6] systems for cancer therapy strongly correspond to both their end-in-mind therapeutic specificity as well as to the complex biochemical and biophysical *in vivo* obstacles the systems must overcome to achieve their desired goals. First, the end-in-mind therapeutic goal of targeting specific neoplastic sites is two-fold: (1) to reduce systemic distribution of the cytotoxic components of the system in order to reduce toxic systemic side effects,

and to (2) reduce overall dosage via localized therapy [37], even by factors as great as 100 [6]. Reducing the dosages may allow more expensive therapeutics to be used in such systems, which may have been avoided otherwise [27].

Secondly, some of the complex biochemical and biophysical *in vivo* obstacles include:

- Clearance (opsonization then phagocytosis) by the reticuloendothelial system (RES), also known as the mononuclear phagocyte system (MPS), which consists of the liver, spleen, lungs and bone marrow [6]
- Creating a system that is biocompatible and biodegradable yet effective [6]
- Protective exclusion via the blood-brain barrier, vascular endothelium [10], and the zonulae occludentes of the kidney tubules [5]
- Magnetic nanoparticle effective size difficulties for proper distribution for desired targeting and hyperthermia effect as well as and post-therapeutic clearance after magnetic field is removed to prevent embolization of blood vessels at target site from magnet pooling or toxic responses over time [27, 29, 30, 37]
- Translating animal study parameters into parameters useful for human clinical application due to size and depth variances of tumor mass [27, 37]
- Neovasculature is heterogenous, with areas of dense vascularization as well as necrosis or hemorrhagic features, which increase the "leakiness" of tumor vasculature [6]
- Increased osmotic pressure of cancer lesions, especially in mature stages [35, 42], which causes extravasation of therapeutics from the tumor intersitium [35]
- Agent/Polymer/Carrier Complexes that are larger and/or have stronger bonds are slower to dissociate (delivery therapy) at the target site [37]
- Multi-drug resistance (MDR), primarily due to overexpression of the plasma membrance P-glycoprotein (Pgp), which is capable of extruding generally positively charged xenobiotics, including some anticancer drugs, from the cell [6]
- Targeting moieties—not the anticancer agents—causing cytotoxicity upon degradation at cellular level [6]

Just as neoplastic masses have unique neovascularization, the tumorous cells possess unique characteristics, which have to be considered for proper/adequate treatment. For example, cancer cell membranes typically have larger numbers of certain types of receptors or cell membrane antigens, which can be located by specific ligands or antibodies, respectively. This has lead to the creation of nanoparticle systems conjugated to such complementary molecules. One example includes neoplastic cell membranes' over-expression of folate receptors, which allows folate-

conjugated nanoparticles to target such cells and is one of many ways to home in on abnormal cells [6, 51, 52].

Thus, an optimized magnetic nanoparticle system would address all of the above obstacles (as well as other not mentioned above or new ones found) and take advantage of the characteristics unique to specific neoplastic cells in order to maximize efficacy per therapeutic dose. With many unique properties depending on the type of cell, and many possible therapeutics, the possibility exists for creating thousands of nanoparticle systems tailored to a specific type of cancer treatment. Creating such optimized systems is extremely difficult, as the above obstacles are no easy task to overcome and require extensive collaboration from experienced scientists in various branches of chemistry, physics, and biology.

So far, such interdisiciplinary collaborations have lead to two basic structural schemes for magnetic nanoparticle delivery systems: liposomes and biodegradable polymeric moieties [31]. Liposomes are hydrophobic phospholipids that form enclosed spherical-like shaped membranes when in the presence of excess water. The size ranges from 50nm to several micrometers, with the optimal preparation using the smallest particles [33]. Drugs may be inside the spheres in aqueous suspension or be located in the bilayer, depending on the hydro-philic/phobic properties of the drug [33]. Biodegradable polymer systems are spheres if solid or capsules if there is an aqueous cavity with a polymer wall, which can be made of various components such as starch, albumin, polylactic acid or polyalkylcyanoacrylate [6, 33]. Unlike liposomes, polymeric nanoparticle systems have been shown to alter the drug release mechanism and maintain stability in biological media [38].

In his review, Cancer Nanotechnology: Opportunities and Challenges, Mauro Ferrari includes a diagram of a multi-functional nanoparticle, which appears in Figure 1 below [10].

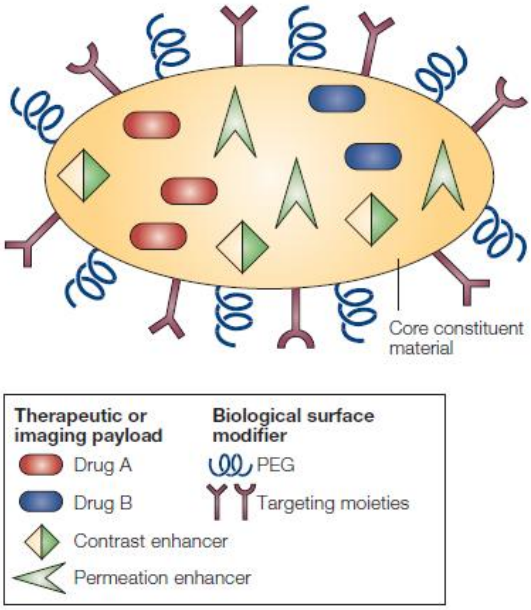

Figure 1. Multi-functional nanoparticle. The diagram illustrates the ability of the system to carry at least one therapeutic agent, contrast enhancers for MRI analysis, permeation enhancers to overcome endothelial tight-junctions, targeting via recognition molecules like folic acid or conjugated antibodies, or polyethylene glycol (PEG) to avoid phagocytosis by the RES [10].

Magnetic nanoparticle systems are variations on this basic structural theme [8, 17] in an attempt to approximate the optimized system described above, in which the contrasting agent is usually magnetite nanoparticles, which are also used for hyperthermia treatments with an applied magnetic field. The overall system approaches optimization by addressing as many biological aspects—obstacles or advantages—as possible including taking advantage of neoplastic cells' unique biochemical and biophysical characteristics.

Avoiding Clearance by RES/Increasing Circulation Time

For example, just by using nanospheres in gene therapy, it has been shown that conjugated nanospheres enhance intracellular uptake and protection of oligonucleotides (ODNs) from intracellular breakdown leading to higher intracellular concentration of intact ODN and thus more efficient antisense activity [6]**.** Also, polymeric systems have been shown to increase circulation time by resistance to opsonization reactions and macrophagic clearance by enhancing biocompatibility through conjugated polymers like dextran or polyethylene glycol (PEG) [8, 51, 52].

Biocompatibility/Biodegradability and Therapeutic Effectiveness

In addition to increased biocompatibility, therapeutic systems must be biodegradable or removable in order to be administered *in vivo* [6]. Such experiments, though clinically inapplicable, may allude to any one of the complex mechanisms of delivery, dissociation, cellular-uptake at tumor sites, many of which are largely unknown.

Passing through NanoBarriers

Once biocompatible and biodegradable, nanoparticle systems may be limited by the blood-brain barrier, vascular endothelium, and kidney tubules, if such therapy is required in those regions. To overcome the blood-brain barrier and vascular endothelial obstacles, nanoparticle systems can respectively alter their core material properties [9, 10, 20, 21, 36, 44] and co-administer a bradykinin antagonist [10, 49]. The zonulae occludentes have cell-to-cell junctions of less than 1nm wide [5], so thus far, delivering the larger nanoparticles to this intracellular space remains an obstacle.

Magnetic Nanoparticle Sizes for Safe Yet Effective Treatment

Another important biocompatibility aspect of magnetic nanoparticle systems is related to the effectiveness of treatment, which is the use of iron oxide (usually Fe_2O_3 and Fe_3O_4) particles classified as either paramagnetic or superparamagnetic, with the latter classified as ≤ 20nm in diameter [5, 37]. The superparamagnetic particles are preferred for *in vivo* application as they require a smaller magnetic field to generate heat for hyperthermic therapy [37]; may be better able to target brain tumors [40], by even crossing the blood-brain barrier (xiii); and they do not retain magnetism after removal of the field [5], which would theoretically prevent iron accumulation in the system and thus any chance of chronic toxicity if high doses of such fluids were administered over long periods of time [48].

However, the first studies conducted on humans by Lübbe and associates lead the group to suggest that larger particle sizes (>100nm) would be more effective in treating tumors [30]. Thus, there is considerable debate about the pros and cons of particle size with respect to the size of the magnetic field required to generate sufficient hyperthermic state to cause damage to the tumor cells but not to the surrounding healthy tissue. Larger particles require more field for the hyperthermic effect, which has been shown to cause deleterious effects in other parts of the body, including stimulation of the peripheral and skeletal muscles, the heart—possibly causing arrhythmia—or non-targeted inductive tissue heating [37].

Animal Model Parameters not at Applicable for Humans

In addition to particle size, the size of parameters used in animal studies are not scaled to human cases and thus are inadequate for clinical use. For example, the size and depth of tumors in human bodies is much different than in small animals tested in the laboratory [37]. Deep-tissue tumors would have to have field strengths so strong that they would likely induce toxic effects to other parts of the body [37]. The limitations to such applications will have to be set by research findings from human trials or sufficiently scaled up from investigations with animals using sophisticated mathematical models, since the former has ethical implications.

Overcoming Neovasculature "Leakiness" and High Osmotic Pressure

Despite the obvious limitations of applying magnetic fields of certain strengths, there are many advantages, including improving the concentration of nanoparticle therapeutics in the leaky, high-pressured tumor regions. This improvement is most obvious when the magnetic field can be within 0.5cm of the tumor surface, as in the early Lübbe experiments [29, 30].

System Complexity Pros and Cons

The more multi-dimensional the system is, the greater the probability of administering the drug, as long as a balance is achieved. For example, the larger the complex, the slower the diffusion of the agents to the site. Also, the stronger the bond between the complex and the agent in the biological fluid media, the more stable the molecule is and higher likelihood of getting the agent to the target site, but the slower the active therapeutic release. Slower delivery may be preferred, for a time-release enhancement of the drug, for example.

Reversing Multi-drug Resistance

Another issue to consider is multi-drug resistance, or MDR, which is primarily due to overexpression of the plasma membrance P-glycoprotein (Pgp), as mentioned above [6].

Pgp ejects usually positively charged xenobiotics, including some anticancer drugs, from the cell [6]. One way to solve this dilemma is to "mask" the positive charge of the sugar on the drug by linking it covalently with the polymer such that the Pgp are fooled into letting the molecule pass through the cell membrane [6]. Dissociation is slower at the target site, as stated above. Reversing agents like amiodarone or verapamil have been simultaneously administered with the nanosphere-encapsulated anti-cancer drug doxorubicin, and cytotoxic effects were measured but overcome by encapsulating both the anti-cancer drug and the reversal agents [6].

Avoiding Unintended Polymer-Induced Cytotoxicity

Other cytotoxic effects noted were from the biodegradable conjugated polymers or detergents upon intracellular or intercellular degradation after the anti-cancer drug dissociated from it *in vitro* [6]. Thorough studies of polymer-induced cytotoxicity will allow selection of biocompatible polymers that will only carry out their carrier function for *in vivo* application.

Designing a magnetic nanoparticle system that addresses the above hurdles allows such systems to function well at the target cell level. The system's functions begin upon systemic administration. Once in the system, the multi-faceted complexes can be used in imaging; can target delivery of the agents to the neoplastic cells; and can induce hyperthermic states at the tumor cell level.

Functions of Magnetic Nanoparticles for Cancer Therapy

Administration

The magnetic nanoparticle systems are submicronic colloidal systems, usually composed of a biocompatible ferrofluid. These fluid systems are injected into the patient intra-tumorally or via the circulatory system feeding into the tumorous region, either intra-venously or intra-arterially while a high-gradient magnetic field is applied specifically over the tumor region in order to concentrate the complex at that site and maintain it there (see Figure 2 below) [27]. Upon concentration, the drug, radionuclide or gene can be released from the complex by whatever mechanism governs that specific system. Often the release mechanism is related to enzymatic activity, pH, osmolality or temperature, and subsequent uptake by the tumor cells can occur [1].

Imaging—Tumor Biomarking

Once administered, magnetic nanoparticle systems can serve as contrast agents for magnetic resonance imaging (MRI) used for diagnosis, pre-surgical mapping, treatment planning and post-treatment analysis. Magnetic contrast agents enhance MRI scan resolution by shortening the net magnetic moment relaxation times of a large group of protons in the presence of an applied magnetic field, B_0, relative to the relaxation times without the magnetic particles [37].

The signal generated by the relaxation is captured via resonant absorption by applying a pulsating magnetic field in a plane orthogonal to B_0 and at the Larmor precession frequency, $\omega_0 = \gamma B_0$ [37]. The gyromagnetic constant, γ, is 2.67×10^8 rad s^{-1} T^{-1}, and in an applied field of 1T, the Larmor precession frequency correlates to a radio frequency field $\omega_0 / 2\pi = 42.57$ MHz [37]. The radio

frequency field is applied in a pulsed fashion long enough to generate a response from the protons' net magnetic moment. When the pulse is off, the magnetic moment relaxation is measured from the induced currents generated in coils in the MRI apparatus [37].

For an applied field, B_0, in the z-axis, the relaxation signals following the following mathematical forms and reflect in which direction(s) they occur [37]:
$m_z = m\ (1 - e^{-t/T1})$ and $m_{x,y} = m \sin(\omega_0 t + \phi)\ e^{-t/T2}$, where ϕ is a phase constant, and T^1 and T^2 are the longitudinal and transverse magnetic moment relaxation times, respectively. The longitudinal relaxation, T^1, occurs as heat loss and measures the amount of dipolar coupling of the proton moments to their surroundings, while transverse relaxation is driven by loss of phase due to fluctuating moments interfering with each other's phases [37].

A couple of the many experimental examples of successful imagery include using long-circulating dextran-coated iron oxide (LCDIO) particles and Sinerem®, the latter of which is part of the class of "ultrasmall superparamagnetic iron oxides," or USPIOs, since the nanoparticles are smaller than 50nm. LCDIO particles were investigated *in vivo* in malignant brain tumors of rats and was taken up sufficiently to provide improved delineation of the tumors in the MR scans [6, 32, 53]. Micrometastases located outside the tumor region were also enhanced by the LCDIO particles [6, 53], which are promising results for diagnostic applications. Sinerem® was also employed in brain tumor detection and was found to deliver precise resolution of the tumor site for an extended period of time, significantly outperforming the typically-used contrasting agent gadolinium chelate, which produced blurry imagery of the brain tumor margins [6, 9]. Improvements such as these suggest great potential for diagnosis biopsies and pre-surgical mapping techniques (see Figure 2 below) [6].

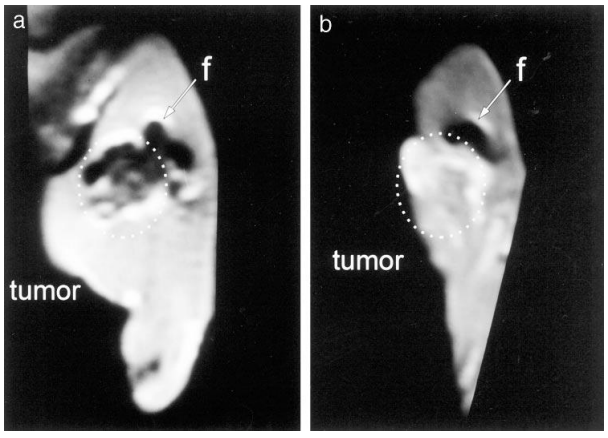

Figure 2. MR Images of Intra-arterial vs Intravenous Injections. MRI of VX-2 carcinomas in hind limbs of rabbit subjects exhibiting concentrations of ferrofluids in targeted tissues one hour post exposure after (a) intra-arterial injection and (b) intravenous injection [1].

In addition to diagnosis and mapping potential, some research has shown a positive correlation with LCDIO uptake and tumor growth (doubling) time [6]. Thus, magnetic nanoparticles could contribute to MRI analysis of *in vivo* neoplastic growth kinetics [6], which could help model treatment programs based on growth timelines generated from kinetics data.

Another very important use for imagery is post-treatment analysis of tumor sites. The magnetic nanoparticle systems are able to fulfill their multi-functional "destiny" by targeting the tumor region, providing a map for diagnosis and treatment and/or delivering the therapeutic package, and finally showing the neoplastic region in remission. Thus, according to research evidence, MRI analysis with magnetic nanoparticles can be used to assay the malignant tissue regions post therapy in order to making conclusions about therapeutic success [1, 22, 43].

Targeted Delivery

The types of materials that the magnetic fields aim to concentrate at the tumor site are anti-cancer drugs, radionuclides, immunostimulants, and/or genes, depending on the tumor type and treatment approach. The wide variety of chemotherapeutics that have been investigated in magnetic nanoparticle therapy include a long laundry list of materials including the drugs doxorubicin [27] and mitoxantrone (see Figure 3 below) [1, 2, 22], immunostimulants, such as tumor necrosis factors [14, 16, 27]; radionuclides Yttrium-90 and Rhenium-188 [37]; and genes, such as heat shock protein 70 (hsp70).

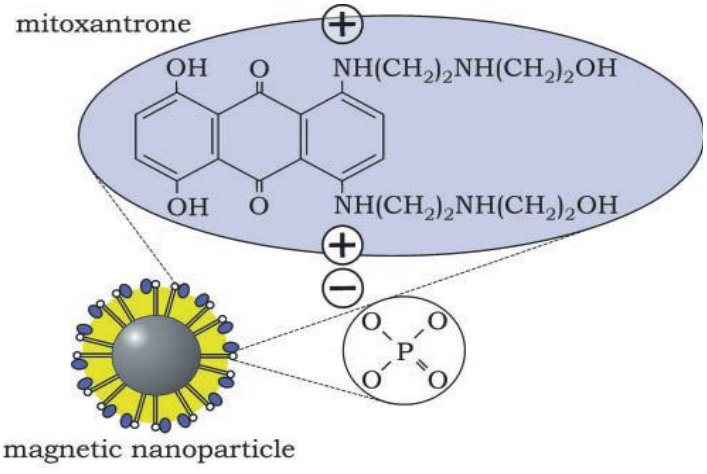

Figure 3. Mitoxantrone (MTX) bound to a magnetic nanoparticle [1].

Delivery of anti-cancer drugs to the tumor sites seems an obvious targeted-delivery function of nanoparticles, but making use of enzymes or other biological factors to stimulate the body's immune

response to the tumor [16, 17, 46], employing radionuclides to provide localized radiation treatments [37], or delivering genes to generate therapeutic responses [15] comprise quite an amazing set of therapies, especially given research evidence of successful application, which should eventually lead to human clinical trials and later routine clinical application.

And it does not stop at the delivery packages. In addition to the biophysical targeting that magnetic nanoparticles can provide, other materials may be complexed with the magnetic nanoparticles to provide a biochemical mechanism to enhance the biophysical targeting. These biochemical targeting agents can be substrates to target surface receptors [4, 22, 51, 52], antibodies to target antigens [8, 39], or clotting identifier complexes [43], all of which home in on neoplastic cell membranes.

The biophysical targeting that the magnetic particles contribute to the therapy system is made possible by the magnetic force exerted on a superparamagnetic (SPM) nanoparticle by a magnetic field gradient [37]: $F_m = V_m \Delta\chi \nabla (B^2/2\mu_0) = V_m \Delta\chi \nabla (\frac{1}{2} B \bullet H)$, where V_m is the particle volume, $\Delta\chi = \chi_m - \chi_w$, which is the effective susceptibility of the magnetic particle in aqueous solution. The magnetic susceptibility, χ, is equal to M/H, where magnetization, M, equals m/V, the ratio of the magnetic moment to the volume of the material, and H is the magnetic field strength [37]. The symbol ∇ designates the differential of some quantity, and the constant μ_0 is the permeability of free space, which is $4\pi \times 10^{-7}$ Tm/A [37]. B is the magnetic induction, such that $B = \mu_0 (H + M)$ [37]. Thus, the magnetic force is proportional to the differential of the magnetostatic field energy density, $\frac{1}{2} B \bullet H$ [37]. When $\Delta\chi > 0$, the magnetic force acts in the direction of the sharpest magnitude increase of the energy density [37]. For more detail on physical relationships, several reviews can be read [11, 13, 37, 50].

Various physical and physiological parameters govern targeting effectiveness. The physical parameters include magnetic field gradient and strength, the magnetic particle properties and volume [37]. Hydrodynamic parameters like blood flow rate, ferrofluid concentration, injection path and circulation duration affect targeting success as much as physiological parameters such as distance of tumor site from the magnetic field source, strength of the agent/polymer/particle binding, and tumor volume [28, 37].

The types of magnets used are usually strong permanent magnets like Nd-Fe-B, and the highest field gradient and strength are formed by using the smallest particles possible with the magnet source as close to the target site as possible [37, 6]. Despite particle size preference of the superparamagnetic particles, Lübbe's experiment above and others have suggested that larger

particles are more effective, especially when administration occurs in larger vessels with larger hydrodynamic magnitudes [29, 30, 37]. This is consistent with mathematical expressions that describe the underlying physical principles.

For example, the magnetic force, F_m, discussed above, has to overcome the hydrodynamic drag force, $F_d = 6\pi\eta R_m \Delta v$, where η is the viscosity of the biological fluid media (water), R_m is the radius of the magnetic particle, and $\Delta v = v_m - v_w$, is the difference between the magnetic particle velocity and that of the biofluid [37]. The velocity of the particle relative to the fluid media, Δv, is equivalent to $[(R_m^2 \Delta\chi)/(9\mu_0\eta)](B^2) = (\xi/\mu_0)\nabla(B^2)$, where ξ is the "magnetophoretic mobility" of the particle and describes how much a particle can be modulated [37]. Thus the larger the particle, the greater the ability to manipulate the particle, which physically explains Lübbe's Phase I trial data suggested.

Recent research suggests that magnetic flux densities must be at range of 0.2T with field gradients of 8 Tm^{-1} for femoral arteries and >100 Tm^{-1} for carotid arteries [47]. On the other hand, target sites with slower blood flow rates should allow smaller particles and/or smaller magnitudes of magnetic flux and field gradients to achieve the desired targeting, which suggests that therapeutic system profiles should change according to each case's unique parameters.

Hyperthermia–Catabolism/Ablation Therapy

The potential of using iron oxides and magnetic fields to induce hyperthermic states to cook malignant tumors dates back to the Gilcrest experiments in 1957 [5, 12, 37]. Gilcrest's group heated tumors of varying sizes with γ-Fe_2O_3 nanoparticles 20-100nm in diameter submitted to a 1.2MHz magnetic field [12, 37]. Since the Gilcrest experiments, many research groups have explored a multitude of magnetic particle systems that are variations on the structural theme described above, and to these variations, different field strengths and frequencies have been applied [37] in the search for an optimized treatment system that addresses as many of the obstacles described above (and others discovered) and takes advantage of, where possible, the biochemical and biophysical properties of the treatment environment. Other groups have built devices to induce therapeutic hyperthermia via magnetic nanoparticles (see Figure 4 below) [12, 18, 37].

Hyperthermia is possible after the superparamagnetic particles (ferrofluid) are injected into the target site directly or into nearby vasculature while applying a strong permanent magnet over the target area to concentrate the particles at the target region. Then an alternating magnetic field of sufficient strength and frequency is applied, which causes energy loss from the particles in the form of heat, which transfers to the tissues in which the particles are amassed [37]. If the tissue

temperature can remain above the "therapeutic threshold" of 42°C for at least 30 minutes, the cells lyse. Hyperthermia induced from magnetic particle systems is promising in that it can confine the treatment to the target tissue, preventing unwanted non-specific thermal ablation of healthy tissue [37].

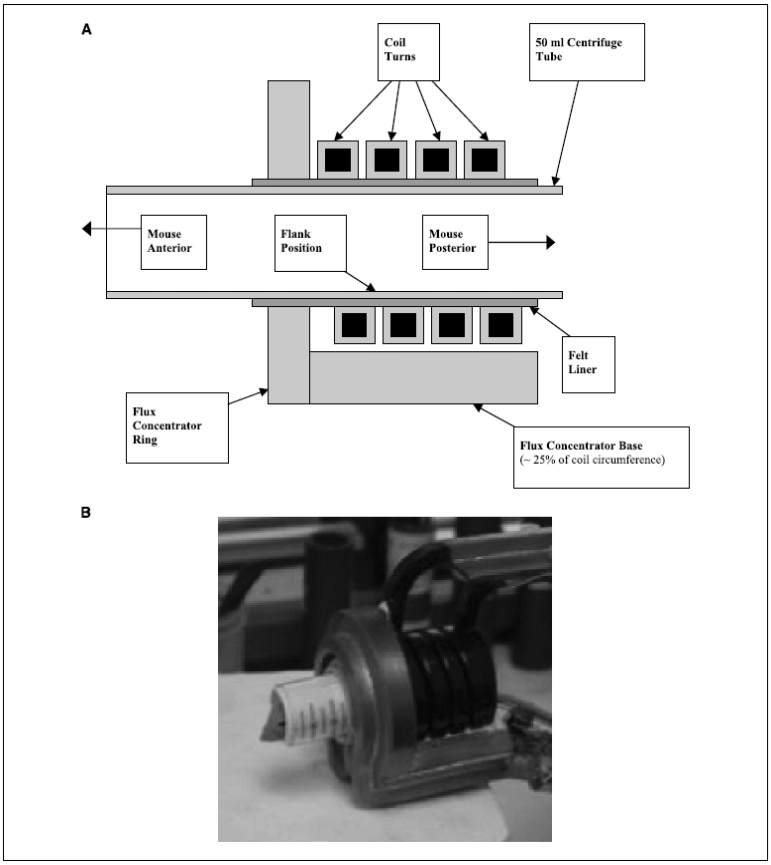

Figure 4. Inductor schematic and photograph. (A) Inductor cross section exhibiting coil, flux concentrator ring and base, conical tube and lining. (B) Murine subject in inductor prior to AMF exposure [18].

Numerous studies on animal models have strong evidence supporting hyperthermic treatments to remove malignancies, especially when the nanoparticle systems are conjugated with targeting and/or anti-cancer agents (see Figure 5 below) [8, 14, 15, 16, 17, 18, 24, 46]. The "usable" range of frequencies and magnetic field amplitudes is considered to be f = 0.05–1.2 MHz and H = 0–15 kAm^{-1}, respectively, and is considered safe and tolerable when $f \bullet H$ does not exceed 4.85 x 10^8 $Am^{-1}s^{-1}$ [33, 37]. Heat deposition rates of 100 mW cm^{-3} of tissue are considered sufficient for thermal ablation [37]. Magnetic field strengths of 0.5-0.8 T were used at distances of at most 0.5cm from the target site in the Lübbe Phase I/II human trials [27, 30]. Since the magnetic fields were not implicated for inducing ill side effects, this range may be used as a heuristic due to the lack of human evidence at this point.

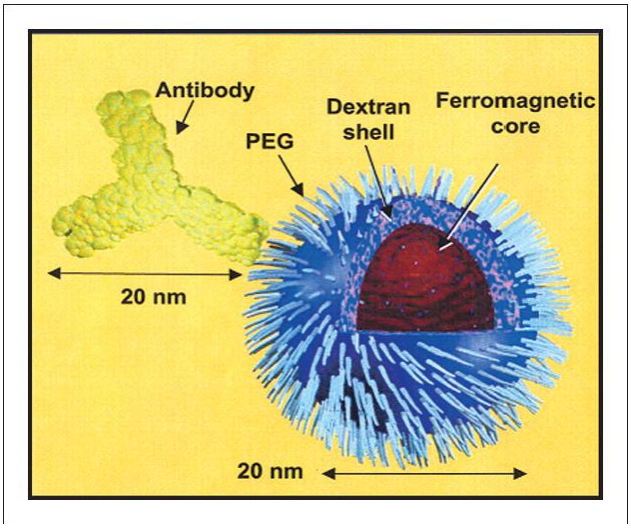

Figure 5. Bioprobe schematic. Bioprobes for AMF thermal ablation of malignant cells were constructed from 111In-DOTA-ChL6 mAb bound to polyethylene glycol (PEG) on dextran-coated iron oxide magnetic nanoparticle spheres [8].

Despite the compelling animal model evidence for hyperthermia, no successful application of this treatment to human cases has been reported [37]. The main constraints were discussed in the sections above: *Magnetic Nanoparticle Sizes for Safe Yet Effective Treatment* and *Animal Model Parameters not at Applicable for Humans.*

Magnetic particles intended for hyperthermic application fall into the ferromagnetic or ferrimagnetic (FM) single domain or multi-domain particles or the superparamagnetic (SPM) classes, each with its own heat-generating mechanism [37]. The craze for magnetic fluid hyperthermia over the last decade employs SPM nanoparticles in an aqueous or organic solvent, making it a ferromagnetic fluid or simply "ferrofluid," the form adopted in this paper [19, 20, 21, 37]. This paper focuses only on SPM nanoparticle applications.

The physical foundation for SPM particle hyperthermia from alternating magnetic fields, AMF, have been reviewed by Rosensweig as well as Pankhurst and associates [37, 41]. The underlying principles are based on the Debye model, which explains that in a finite rate of change of M in a ferrofluid, M lags behind H [7, 37]. In small field amplitudes and with minimal interaction among SPM nanoparticles in a colloidal suspension, a ferrofluid's magnetization is related to an AMF by its complex magnetic susceptibility, $\chi = \chi' + i\chi''$, whose components, χ' and χ'', are dependent on the applied frequency [37]. The susceptibility component, χ'', reflects the out-of-phase portion and results in heat generation, which takes on the following relationship [37]: $P_{SPM} = \mu_0 \pi f \chi'' H^2$. Since M

lags H, magnetic energy is converted into internal energy [37]. The heat generation from magnetic particles are reported in terms of the specific absorption rate (SAR), in the units W g^{-1} [37].

Particle density times SAR is equivalent to *P* for that particle, which allows for comparison of heat generation ability of a multitude of particle sizes, leading to the fact that SPMs can produce high levels of heating with lower field strengths [37]. Lower field strengths would subject patients to less risk of hyperthermic damage to non-target areas or other side effects, which is why smaller particles are preferred, as was mentioned above in the section *Magnetic Nanoparticle Sizes for Safe Yet Effective Treatment.* Since smaller particles are subjected to hydrodynamic obstacles, the debate for the "perfect" particle size is ongoing, and as mentioned above, different therapeutic approaches will have to be decided upon on a case-by-case basis, after all bio-parameters are considered.

Conclusion

Building magnetic nanoparticle systems to successfully treat cancer is a complex task with many biophysical and biochemical obstacles to overcome. Over the past 50 years, interdisciplinary teams have taken creative approaches to build therapeutic systems that address these obstacles while taking advantage of the unique biochemical and biophysical properties of neoplastic tissues. Many animal model experiments elucidate the potential for magnetic nanoparticle systems to be multi-faceted complexes that could be used in MR imaging for diagnosis, treatment plans, and remission monitoring; targeted delivery of a wide variety of anti-cancer agents from drugs to genes; and selectively eliminate malignancies from the patient's body via magnetic field induced hyperthermia.

Such targeted programs would, in theory, allow cancer patients to be diagnosed earlier, treated faster and maintain a much higher quality of life during and after treatment than that typically experienced by patients undergoing chemo- and/or radiation therapies. Before this dream can be realized, animal model parameters must be scaled up for human application via sophisticated mathematical modeling. Once substantial data exists for human application, clinical trials on humans can begin, followed by approval by the FDA. The FDA approval process may delay magnetic nanoparticle cancer therapies from hitting the market for a number of years since most of these systems have constituents falling under all three categories: drugs, medical devices and biological agents, which may require individual examination followed by collective evaluation [10]. Despite the steep uphill climb, the race toward finding a cure for cancer via SPM nanoparticle therapies is strong and will likely lead to individually-tailored SPM nanoparticle therapeutics that will save millions of lives in the (hopefully not-too-distant) future.

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