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Chapter 3

Laser and Radiofrequency Induced Hyperthermia Treatment via Gold-Coated Magnetic Nanocomposites

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Additional information is available at the end of the chapter

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1. Introduction

Cancer is a disease characterized by unregulated growth of cells. This is caused by damage of deoxyribonucleic acid (DNA) results in mutations to vital genes that control cells divisions *(Albert et al., 2004)*. The most common non-invasive approaches used for cancer treatment represent in chemotherapy, as well as radiotherapy. Chemotherapy uses cytotoxic drugs, which are also known as "anti-cancer" drugs or "anti-neoplastic." On other hand, radiotherapy uses high energy of X-rays which were directed to cancerous tissues to cure or shrink the tumor, as well as to protect the tissue against tumor recurrence. Although chemotherapy and radiotherapy are capable of killing cancerous cell, nevertheless they cause some serious secondary effects including nausea, diarrhea, tiredness and fertility loss *(Johannes et al., 2005)*.The conventional surgery of solid tumors is also an effective therapy for removing of well defined and accessible primary tumors located within nonvital tissue regions. However, this therapy is unsuitable for treatment of ill defined tumors and metastases, as well as tumors that embedded within vital regions *(Hirsch et al., 2003)*.

The current methods for cancer treatment have moderate to severe secondary effects. For this reason, the investigations of new alternatives are essentially. Thermo-therapy is considered one of the most important methods for cancer treatment. In general, the term thermo-therapy refers to both hyperthermia and thermal ablation therapy (*Mriza et al., 2001)*. Hyperthermia therapy is based on the fact that tumor cells are more sensitive to temperature increase than normal tissue cells. It involves tumor heating to temperatures between 41- 42°C inducing almost reversible damage to cells and tissues. For thermal ablation therapy higher temperatures are applied ranging from 50°C to 70°C, leading to destruction of pathologically degenerated cells and irreversible damage resulting in

diminishing, disappearing of the tumors or at least growing stop. Thermal methods include radiofrequency ablation (RFA), focused ultrasound thermo-therapy, laser-induced thermal therapy and magnetic thermal ablation *(Hilger et al., 2002)*.

The thermal therapy can provide a minimal invasive alternative to conventional surgical treatment of solid tumors. In addition, the thermal therapeutic procedures are relatively simple to perform and therefore have the potential to improve recovery times and reduce the complication rates and hospital stays *(Hirsch et al., 2003)*. Although, the thermal methods offer several advantages, nevertheless have some of limitations. For example, the tumor volume and speed of ultra-sound thermo therapy is limited by the potential destruction of normal tissue in the near field between the target and the ultrasound probe. Radiofrequency ablation and microwaves approaches suffer from common limitations that are intervening tissue problems. On other wards, the heating effects from these sources are non-specific. In addition, the energy deposition is often much slower with these moieties serving to increase the treatment time and generate less sharp lesion boundaries *(Ko¨hrmann et al., 2002)*.

To overcome these problems, new techniques in the field of nanoscience, nanotechnology and nanomedicine are now developing into treatment approach based on internal heating of tissue such as magnetic fluid hyperthermia (MFH), which in turn based on internal heating sources. In order to achieve the optimal effectiveness, this approach requires photo-thermal convectors to allow heat production within a localized region at lower incident energies. This requires development of particular particles that have highly magnetic properties such as Super-paramagnetic Iron Oxide Nanoparticles Fe_3O_4 (SPIO NPs). During this approach surrounding healthy cells are capable of surviving exposure to temperatures up to around 46.5°C and more readily able to dissipate heat and maintain a normal temperature while the targeted tumor tissues have a higher thermal sensitivity than normal tissue because of experience difficulty in dissipating heat due to the disorganized and compact vascular structure (reduced blood flow), anaerobic metabolism (acidosis), and nutrient depletion. So an irreversible damage to diseased cells occurs at temperatures in a range from approximately 40°C to about 46°C (Yu-Fen *et al., 2008*).

2. Nanomedicine and magnetic nanomaterials

Nanomedicine stands at the boundaries between the physical, the chemical, biological and medical sciences. It originated from the imaginative idea that robots and other related machines at the nanometer scale could be designed, fabricated and introduced into the human body for repairing malignant cells at the molecular level. According to its original vision, nanomedicine is a process including the diagnosis, treatment and prevention of diseases and traumatic injuries, and the preservation and improvement of human health, using molecular tools and molecular knowledge of the human body (*Freitas 2005*). The progress in both nanoscience and nanotechnology makes nanomedicine practical. From a technical viewpoint, nanomedicine consists of the applications of particles and systems at the nanometer scale for the detection and treatment of diseases at the molecular level, and it plays an essential role in eliminating suffering and death from many fatal diseases, such as

cancer (*Yih and Wei 2005*). Based on nanofabrication and molecular self-assembly, various biologically functional materials and devices, such as tissue and cellular engineering scaffolds, molecular motors and biomolecules, can be fabricated for sensor, drug delivery and mechanical applications (Royal Society and Royal Academy of Engineering 2004). Nanomedicine has obvious advantages. First, nanoparticles are potentially invaluable tools for investigating cells because of their small size. Second, as their size can be controlled, from that of large molecules to that of small cells, the ability of nanoparticles to escape the vasculature *in vivo* can also be controlled. Third, because of their small size, nanoparticles can circulate systemically in the bloodstream and thus serve in roles such as magnetic resonance enhancement, iron delivery for the production of red blood cells and drug delivery to improve the availability of serum-insoluble drugs (*Whitesides 2005*).

2.1. Status of nanomedicine

Nanomedicine has developed in numerous directions, and it has been fully acknowledged that the capability of structuring materials at the molecular scale greatly benefits the research and practice of medicine. However, nanomedicine is a long-term expectation. Before nanomedicine can be used in clinics, fundamental mechanisms of nanomedicine should be fully investigated, and clinical trials and validation procedures should be strictly conducted. Though, it is possible that some biological entities, such as proteins, DNA and other bio-polymers, could be directly used for biosensor applications, nevertheless some serious issues, such as biocompatibility and robustness, may hinder the progress of these efforts. Though in many areas, such as disease diagnosis, targeted drug delivery and molecular imaging, clinical trials of some nanomedicine products are being made, the clinical applications of these techniques, which require rigorous testing and validation procedures, may not be realized in the near future (Royal Society and Royal Academy of Engineering 2004). At all events, it should be noted that although the applications of nanomaterials in biology and medicine are in an embryo stage, it is the great promise of nanomedicine that has inspired researchers to extensively investigate the interfaces between nanotechnology, biology and medicine (*Satyanarayana, 2005*).

2.2. Magnetic nanomaterials

The magnetic nanomaterials used in biology and medicine generally fall into three categories: zero dimensional nanomaterials such as nanospheres; one-dimensional nanomaterials such as nanowires and nanotubes; and two-dimensional nanomaterials such as thin films. Usually, all the nanospheres, nanorods, nanowires and nanotubes are called nanoparticles, among which, nanorods, nanowires and nanotubes are high aspect-ratio nanoparticles. In most of the biomedical applications, magnetic nanoparticles are suspended in appropriate carrier liquids, forming magnetic fluids, also called ferrofluids. Among the three types of magnetic nanoparticles, magnetic nanospheres are most widely used in biomedicine. To realize their biomedical applications, the magnetic nanospheres should be stably suspended in the carrier liquid, and they should also carry out certain biomedical functions. The magnetic material most often used is iron oxides, and the carrier liquids are

usually water, kerosene or various oils. Due to their small size, the magnetic nanoparticles in carrier liquids neither form sediment in the gravitational field or in moderate magnetic field gradients, nor do they agglomerate due to magnetic dipole interaction. However, a stable suspension can only be achieved if the particles are protected against agglomeration due to the van der Waals interaction. Usually this protection can be achieved by one approach is the electric charge stabilization. In this approach, a thin layer of gold is coated on the surface of the nanospheres. Meanwhile, the thin gold layer can also serve as an ideal base on which chemical or biological agents can be functionalized. These molecules generate a repulsive force, preventing the particles from coming into contact and thus suppressing the destabilizing effect of the van der Waals interaction. In practical applications, this approach is often used in combination for the majority of ferrofluids, since this allows the synthesis of suspensions which are stable over years (*Could 2004*).

2.2.1. Magnetic (iron oxide nanoparticles)

Magnetic iron oxide nanoparticles are the most investigated material in biomedical techniques, due to its superior biocompatibility with respect to other magnetic materials, either in form of oxides or pure metals. Several types of iron oxides exist in nature and can be prepared in the laboratory. Nowadays, only maghemite (γ-Fe_2O_3) and magnetite (Fe_3O_4) are able to fulfill the necessary requirements for biomedical applications. These requirements include sufficiently high magnetic moments, chemical stability in physiological conditions and low toxicity, not to mention the easy and economical synthetic procedures available for the preparation of these materials *(Neuberger et al., 2005)*.

The degree of atomic order in the iron oxide lattice, or in other words its degree of crystallinity, as well as the dispersity of the nanoparticles in terms of size and shape are critical parameters that affect their performance in diagnostic and therapeutic techniques as a contrast agent in magnetic resonance imaging (MRI) and hyperthermia, respectively. These parameters are strongly correlated to the approach for their synthesis *(Maenosono et al., 2008)*.

2.2.2. Synthesis of iron oxide nanoparticles

The common existing methods to synthesize the iron oxide nanoparticles are physical, chemical and biological methods. Comparatively, chemical methods, especially wet chemical ones are much simpler and more efficient *(Gupta et al., 2004)*. Several synthetic procedures have been developed to synthesize iron oxide nanoparticles. The simplest, cheapest and most environmentally-friendly procedure is based on the co-precipitation wet chemical method, which involves the simultaneous precipitation of ferrous (Fe^{2+}) and ferric (Fe^{3+}) salts in an alkaline medium *(Kang, 1996)*. So the synthesis of iron oxide nanoparticles with an expected size distribution and stability of suspension is no longer the biggest challenge for researchers. The key issue now is how to achieve the aim of stealth of these nanoparticles in blood circulation and to attach them on desired sites for *in vivo* or *in vitro* applications *(Sun, 2006)*.

Hydrothermal synthesis techniques are an alternative method for the preparation of highly crystalline iron oxide nanoparticles *(Wang et al, 2005)*. In this case a mixture of iron salts dissolved in aqueous media is introduced in a sealed Teflon container and heated above the boiling temperature of water, and consequently the reaction pressure is increased much above atmospheric pressure. The synergistic effect of high temperatures and pressures strongly improves the quality of the nanocrystals and hence their magnetic features. However, and in contrast to the biological technique, there is no straightforward way to control the size and the shape of the final particles and usually polydisperse samples are obtained.

Biological methods, since nanomaterials have comparable dimensions to biological aggregates, bio-related synthesis methods have been explored for novel nanoparticle synthesis. In biological methods, synthesis and assembly of crystalline inorganic materials can be regulated by biological organisms under environmentally benign conditions and desired chemical compositions and phases can be achieved. For example, the nucleation of semiconducting nanoparticles can be initiated in the presence of viruses expressing material-specific peptides. Other examples are the use of porous protein crystals, manipulation of bacteria to produce oxide nanoparticles and selection of metal-specific polypeptides from combinatorial libraries *(Reiss et al. 2004)*. In biological methods, biological entities usually serve as templates for nanoparticles formation. In all cases, the biological entities were used not only to encapsulate the nanoparticles, but to strictly regulate the dimension of the crystals. To prepare magnetic nanoparticles, ferritin can be used which consists of 24 nearly identical subunits. Self-assembly of ferritin will form a spherical cage with a 7.5–8.0 nm-diameter cavity, which can be used for the biological storage of iron in the form of ferrihydrite, an iron (III) oxy-hydroxide? The protein cage is able to withstand relatively high temperatures for biological systems (up to 65 ◦C) and various pH values (~ 4.0–9.0) for certain periods of time. Therefore this protein template is quite strong and will not cause any significant disruption of the quaternary structure.

2.2.3. Classification of iron oxide nanoparticles

There are many categories of iron oxide nanoparticles based on their overall diameter (including iron oxide core and hydrated coating). Iron oxide nanoparticles can be distinctly classified into super-paramagnetic iron oxide nanoparticles (SPIO NPs) between 300 nm and 3.5 μm; standard SPIO (SSPIO) of approximately 60–150 nm; ultra small SPIO (USPIO) of approximately 10–40 nm (*Weissleder et al., 1990)*; monocrystalline iron oxide nanoparticles (MION—a subset of USPIO) of approximately 10–30 nm and cross-linked iron oxides (CLIO) which is a form of MION with cross-linked dextran coating (*Shen et al., 1993)*.

On the other hand, the magnetic materials are characterized by the presence of magnetic dipoles generated by the spinning of some of their electrons. Each of these polarized electrons can be aligned in a parallel or antiparallel fashion with respect to the neighboring ones in the crystal lattice, and this type of interaction is what gives rise to the macroscopic magnetic effect that we can measure. Based on the magnetic response, the magnetic

materials can be classified into; diamagnetic, paramagnetic, ferromagnetic, ferrimagnetic, anti-ferromagnetic and super-paramagnetic *(Cozzoli et al., 2006)* as shown in Fig (1).

Diamagnetic materials are characterized by coupled or paired magnetic dipoles, so there is no permanent net magnetic moment per atom. That is to say that these materials have not any interactions or slightly repelled with the magnetic field. The magnetic susceptibility of these materials is negative and independent on temperature.

Paramagnetic materials characterized by randomly oriented (or uncoupled) magnetic dipoles, this can be aligned only in the presence of an external magnetic field along its direction. This type of material has neither coercivity nor remanence, which means that when the external magnetic field is switched off the internal magnetic dipoles randomize again. No extra energy is required to demagnetize the material and hence the initial zero net magnetic moment is spontaneously recovered.

Ferromagnetic materials characterized by individual magnetic dipoles in a crystal, those can align parallel one to the other, hence exhibiting an enhanced collective response even in the absence of an external magnetic field. This is what is known as *ferromagnetism*. Beside strong intensity of magnetization, the fundamental property of ferromagnetic solids is their ability to record the direction of an applied magnetic field. When the magnetic field is removed, the magnetization does not return to zero but retains a record of the applied field.

Ferrimagnetic and anti-ferromagnetic materials, in contrast to the ferromagnetic situation, neighboring magnetic dipoles can align antiparallel in the lattice, which means that they will cancel each other i.e. repulsion of magnetic dipoles . This type of magnetic exchange can lead to two different situations. The first is *ferrimagnetism;* when the two coupled spins show different values, and in that case a net magnetic dipole different than zero will still magnetize the material even in the absence of an external magnetic field. While the second is *anti-ferromagnetism;* when the magnetic dipoles or interacting spins have the same value and hence the material shows a net zero magnetization. The latter case lacks of interest for biomedical applications due to zero net magnetic moment arising in such materials.

Super-paramagnetic materials, bulky sized particles of magnetic materials such as (Fe), (Co) or (Ni), as well as some of their alloys (FePt & FeCo) have ferromagnetic properties due to their multi-domain structures of the particles. In contrast, at the nanometer scale of approximately 14 nm, the multi-domain combined together forming a single domain crystal, which is classified as super -paramagnetic *(Schmidt, 2001)*. Super-paramagnetic iron oxide nanoparticles are special class of paramagnetic materials which combine ferromagnetic and paramagnetic properties due to high magnetic moments which are observed under the effect of a magnetic field, but no remanent magnetic moment will be present when the external magnetic field is removed. This property translates into a significant advantage especially *in vivo* experiments, where the absence of coercivity or in other words the zero net magnetic moment of the nanoparticles after concluding the diagnostic measurement or the therapy will prevent the potential aggregation of the particles that could easily cause the formation of embolisms in the blood vessels (*Thorek et al., 2006)*.The path of magnetization

M as a function of applied field H is called a hysteresis loop or M-H curve as shown in figure (2).

2.2.4. Characteristics of magnetic nanomaterials for in vivo bio-applications

When nanoparticles are used for *in vivo* applications, the nanoparticles have to stay with nil or minimal side effects. Therefore, complete characterizations of the particulate system are essentially to make a decision whether the use of nanocarriers systems are appropriate for specific *in vivo* applications or not. The nanoparticles can be described by the following physicochemical properties according to their distribution within the body system: size distribution, surface charge modification ,targeting, cellular uptake, bio-stability, metabolism, toxicity, capacity for protein adsorption, surface hydrophobicity, rate of loading , release kinetics, surface characteristics, density, porosity, degeneration of carrier system, cristallinity, density, mobility and the molecular weight *(Neubergera et al., 2005)*.

2.2.4.1. Size distribution

Most intravenous administrated nanoparticles are recognized as ''foreign'' from the body system and are eliminated immediately through macrophages of the mononuclear phagocytosis system (MPS) depending on the size. The size of particles usually refers to the total diameter of the particles including the core and the coating layer. It is well known that, the smallest diameter of capillaries in the body is 4 μm. So, NPs smaller than 4μm are taken up through cells of the reticuloendothelial system (RES) mainly in the liver (60–90%) and spleen (3–10%). While small particles up to 150 nm will be phagocytosed through liver cells. There is a tendency for particles larger than 200 nm to be filtered by the venous sinuses of the spleen, as well as will be captured and withheld in the lungs. In general, the large particles are eliminated faster from the blood, and have short plasma half-life-period compared to the small particles (*Muller et al., 1997)*.

2.2.4.2. Surface charge and protein adsorption

Particles with large sizes and/or aggregations of small particles such as magnetic nanoparticles (MNPs) may be trapped causing emboli within the capillary bed of the lungs. Therefore, it is important to know the surface charge and aggregation behavior of the particles in the blood circulation system *(Neuberger et al., 2005)*.

All bare nanoparticles are unsuitable for *in vivo* applications, where the particle surface would be exposed to a biological environment and oxidized during application. Using bare nanoparticles directly, this could damage its structures and its properties. On the other hand, nanoparticles in solid phase cannot be injected into human body. So, before injection NPs have to be dispersed to hydrophilic solvent via specific interaction between the nanoparticles surface and surfactants *(Harisinghani et al., 2003)*.

The surface charge also plays an important role during endocytosis process. There should be a slower uptake for negatively charged particles due to the negative ''rejection'' effect of the negatively charged cell membrane. However, the endocytosis index *in vitro* is minimal with

a zeta potential close to zero. In contrast, Phagocytosis process is increased with a higher surface charge independent of whether the charge is negative or positive. The higher the surface charge the shorter is the residence time of nanoparticles in the circulatory system *(Neuberger et al., 2005)*.

The adsorption of proteins at the particle surface is called *"opsonization"*. This phenomenon results from immediate interaction between nanoparticles with plasma proteins after intravenous injection .The amount of adsorbed proteins is based on the size of the molecules, as well as the surface charge of the particle, where the capacity of protein adsorption increases by increasing size and charge of the particles. The adsorbed protein components play an important role in the biodistribution, degradation and elimination of the nanoparticles. Therefore, the treatment method of the nanoparticles surface must be addressed *(Muller et al., 1997)*.

The surface charge and protein adsorption capability are more related to the surfactants bond to the nanoparticles surface. There is another important role of surfactants on nanoparticles, when the NPs are injected into human body as contrast agents, these nanoparticles must locate the targeting area accurately and rapidly. Appropriate surfactant could achieve such objective. Some experiments *in vitro* already proved folate-mediated nanoparticles composed of ploy ethylene glycol (PEG) / poly ε-caprolactone have potential of tumor cell-selective targeting *(Gee et al., 2003)*.

2.2.4.3. Targeting

All *in vivo* applications require that the NPs should accurately localize to therapeutic sites. All targeting methods could be classified to passive, active and physical targeting. The physical targeting is the localization of the nanoparticles with external assistance, typically by applied magnetic field from outside of the body; the physical targeting has less capability to recognize specific cells or tissues. The passive targeting based only on the disrupted endothelial lining of tumor tissues; enhanced penetration and retention (EPR) allows nanoparticles of smaller size to pass, and accumulate in the tumor. In active targeting, specific targeting functional groups, such as monoclonal antibodies, are immobilized on the particle surface to efficiently increase the chance of uptake by specific cells *(Kelly et al., 2005)*.

2.2.4.4. Cellular uptake

Cellular uptake of nanoparticles is another issue that should be taken into account, when considering their use in diagnostic and therapeutic applications. The cellular uptake of nanoparticles is strongly dependent on particle size as it was proven *in vitro* and *in vivo*. In general, small nanoparticles can go deeper into tissue than larger particles and often penetrate the cell itself *(Leslie-Pelecky, 2007)*. Lewinski et al summarized the situation for many types of nanoparticles *(Lewinski et al., 2008)*.

The cellular uptake of nanoparticles occurs through a process known as endocytosis, which can be generally classified into three processes depending on nanoparticles size. Phagocytosis process which is the predominant mechanism for uptake of large particles,

phagocytotic activity increases with size of particles, whereas smaller particles<150 nm can be up-taken by all types of cells through pinocytosis process (cell drinking).The third is non-specific endocytosis or receptor-mediated endocytosis process *(Neuberger et al., 2005)*.Super-paramagnetic iron oxide nanoparticles have been shown to be uptake by a receptor mediated endocytosis process (*Raynal et al., 2004)*.

2.2.4.5. Bio-stability

When nanoparticles are introduced into the body, several aspects can compromise its stability. First of all, the physiological media have different ionic strength as compared with the ultrapure water mainly used in laboratories: increasing the ionic strength of aqueous solution will suppress the electric double layer around the charged particles, resulting in a partial or total aggregation of the system. A similar behavior could be observed by the particles once they enter specific body compartments, due to a variation in pH with respect to the media in which the nanoparticles are initially dispersed. In addition, when nanoparticles are injected in the blood circulation system, a nonspecific adsorption of plasma proteins onto nanoparticles surface *"opsonization"* will occur, this phenomenon is more pronounced for nanometer size particles due to two main effects: the high surface to volume ratio, as well as the attractive forces between the nanoparticles such as magnetic nanoparticles. When this phenomenon occurs, a fast clearance of the nanoparticles is observed. To prevent such effects, several synthetic and natural polymers have been introduced to the nanoparticles surface including PEG and dextrin (*Kohler et al., 2004)*.

2.2.4.6. Metabolism

The metabolism process of the nanoparticles is another issue that should be taken into account. For example, iron oxide nanoparticles can be present in two different oxidation states: the ferrous Fe (II) form which will be oxidized by endogenous molecular oxygen, resulting in the conversion of ferrous iron to ferric Fe (III). Ferric iron is the preferred physiological oxidation state of iron; Fe (III) is highly reactive and can induce catalytic activity that may result in severe oxidative cell damage. As a result, iron carrier proteins and chelates are used to allow for safe transfer of iron from cell to cell within the body, and for safe intra-cellular storage of excess iron. The natural eventual fate of Fe_3O_4 nanoparticles above approximately 200 nm in diameter is to reside in macrophage-rich tissue, such as the liver and spleen (peak concentration at 2 hours after contrast intake).While particles below 10 nm are removed rapidly through extravasations and renal clearance *(Gupta et al.,* 2004).

2.2.4.7. Biocompatibility

Biocompatibility is one of the most important considerations in the development of biomedical applications of nanomaterials. Most of the magnetic nanowires are compatible with living cells. They can be functionalized with biologically active molecules, and they do not disrupt normal cell functions, such as cell proliferation and adhesion, and gene expression (*Hultgren et al. 2005*).

2.2.4.8. Toxicity

The non-cytotoxic, non-immunogenic and biocompatible properties of nanoparticles are important issues for the potential application in nanoimmunology, nanomedicines and nanobiotechnology. When discussing the toxicity of nanoparticles, generalization becomes difficult because their toxicity depends on numerous factors including the dose, chemical composition, method of administration, size, biodegradability, solubility, pharmacokinetics, biodistribution, surface chemistry, design, shape and structure. In general, size, surface area, shape, composition and coating of nanoparticles are the most important characteristics regarding cytotoxicity *(Neuberger et al., 2005)*.

Several *in vivo* studies on animals had shown that, with a large dosage of 3,000 μmol Fe based nanoparticles per kg body weight, the histology and serologic blood tests indicated that no side effects occurred after 7 days of treatment *(Lacava et al., 1999)*.

To minimize the risks posed by nanoparticles, there are two basic avenues. One is to develop new highly biocompatible nonmaterials with low toxicity such as silica nanoparticles. Another one is the surface modification of nanoparticles with biocompatible chemicals such as PEG, dextrin and chitosan. Thus many great efforts are being made to develop nanoparticles satisfactory for biomedical applications *(Cho, 2009)*.

2.2.4.9. Easy detection

As almost all biological entities are non-magnetic, magnetic nanoparticles in biological systems can be easily detected and traced. One typical example is the enhancement of the signal from magnetic resonance imaging (MRI) using magnetic nanoparticles. In this technique, a subject is placed in a large, external magnetic field and then exposed to a pulse of radio waves. Changes to the spin of the protons in water molecules are measured after the pulse is turned off. Tiny differences in the way that protons in different tissues behave can then be used to build up a 3D image of the subject (*Koltsov 2004*).

2.2.4.10. Magnetic manipulation

Magnetic nanoparticles will rotate under an external uniform magnetic field, and will make translational movements under an external magnetic field gradient. Therefore, magnetic nanoparticles, or magnetically tagged molecules, can be manipulated by applying an external magnetic field. This is important for transporting magnetically tagged drug molecules to diseased sites. The magnetic manipulation of magnetic nanowires and nanotubes is important for applying forces to biological entities, and for nanowires or nanotubes to get into biological entities.

2.2.4.11. Energy transfer

Magnetic nanoparticles can resonantly respond to a time-varying magnetic field, transferring energy from the exciting magnetic field to the nanoparticles and the tagged biological entities. This property has been used in hyperthermia treatment of cancer tumors (*Pankhurst et al. 2003*).

2.2.5. Biomedical applications of iron oxide NPs

Nanotechnology, dealing with nanoscale objects, has been developed at three major levels: nanomaterials, nanodevices and nanosystems. At present, the nanomaterials level is the most advanced of the three. Nanomaterials are of great importance both in scientific investigations and commercial applications due to their size-dependent physical and chemical properties. Nanomaterials with various shapes have been developed successfully. Common morphologies are quantum dots, nanoparticles/nanocrystals, nanowires, nanorods, nanotubes, etc. It is desirable to have a full range within the nanomaterial family because many applications demand particular nanomaterials with special structures.

Magnetic nanoparticles, being a sub-family of nanomaterials, exhibit unique magnetic properties in addition to other specific characteristics. Their remarkable new phenomena include super-paramagnetism, high saturation field, high field irreversibility, extra anisotropy, and temperature-depended hysteresis, etc. Research investigation has revealed that the finite size and surface effects of magnetic nanoparticles determine their magnetic behavior. For instance, a single magnetic domain forms when the size of a ferromagnetic nanoparticle is less than 15 nm. In other words, an ultrafine ferromagnetic nanoparticle displays a state of uniform magnetization under any field. Thus, at temperatures above the blocking temperature, these nanoparticles show identical magnetization behavior to atomic paramagnets (super-paramagnetism) with an extremely large magnetic moment and large susceptibilities.

Magnetic nanoparticles have found many successful industrial applications. Recently, tremendous research efforts have been stimulated on the usage of magnetic nanoparticles in the field of biomedical and biological applications.

Understanding of biological processes and hence developing biomedical means have been continuously pursued. These aims are one of strong driving forces behind the development of nanotechnology. The interests on magnetic nanoparticles for bio-applications come from their comparable dimensions to biological entities coupled with their unique magnetic behaviors. Though common living organisms are composed of cells of about 10 μm size, the cell components are much smaller and generally in the nanosize dimension. Examples are viruses (20–450 nm), proteins (5–50 nm) and genes (2 nm wide and 10–100 nm long). Synthetic magnetic nanoparticles have controllable dimensions and just a few nanometer-diameter nanoparticles can be synthesized by carefully designing experimental procedures and controlling experimental conditions. With such a nanoscale dimension, it would be possible for magnetic nanoparticles to get close to a biological entity of interest. Moreover, the interaction between magnetic nanoparticles and biological entities can be adjusted by coating nanoparticles with biological molecules, called bio-functionalization. This offers a controllable means of 'tagging' or addressing the binding at nanoscale. The comparable dimensions and magnetic properties of magnetic nanoparticles have prompted the idea of using them as very small probes to spy on the biological processes at the cellular scale without introducing too much interference. Actually, optical and magnetic effects have been treated as the most suitable approaches for biological applications owing to their non-invasive behavior.

In view of the magnetic properties of magnetic nanoparticles, they can be manipulated by an external magnetic field gradient, which is described by Coulomb's law. Magnetic nanoparticles are able to transport into human tissues due to the intrinsic penetrability of magnetic fields into human bodies. This 'action at a distance' opens up many potential bio-applications including transportation of magnetically tagged biological entities, targeted drug delivery, etc. Another important property of magnetic nanoparticles is their resonant response related to a time-varying magnetic field *(Pankhurst et al. 2003)*. Hence energy transfer from the exciting field to the magnetic nanoparticles can be realized. In this way, toxic amounts of thermal energy are able to be delivered via magnetic nanoparticles to the targeted tumors resulting in malignant cell destruction. This process is named hyperthermia, which will be addressed in detail in this chapter. In addition to the site-specific drug delivery and hyperthermic treatment, magnetic nanoparticles have found other versatile bio-applications such as magnetic bio-separation, contrast enhancement of magnetic resonance imaging, gene therapy, enzyme immobilization, magnetic manipulation of cell membranes, immunoassays, magnetic bio-sensing, etc. *(Sun et al. 2005)*. Each application depends upon the relationship between the external magnetic field and the biological system. Magnetic fields with proper field strength are not deleterious to either biological tissues or biotic environments. In a given bio-application, magnetic nanoparticles are usually injected intravenously into the human body and are transported to the targeted region via blood circulation for biomedical diagnostic or treatment. An alternative means is using magnetic nanoparticle suspension for injection *(Berry 2003)*. It has been well accepted that a desirable magnetic medium should not contain nanoparticle aggregation, which will block its own spread. For this reason, stable, uniform magnetic nanoparticle dispersion in either an aqueous or organic solvent at neutral pH and physiological salinity is required. The stability of this magnetic colloidal suspension depends on two parameters: an ultra small dimension and surface chemistry. The particle size should be sufficiently small to avoid precipitation due to gravitation forces while the charge and surface groups should create both steric and coulombic repulsions which stabilize the colloidal suspensions.

The magnetic properties of magnetic nanoparticles are determined by their elemental compositions, crystallinity, shapes and dimensions. Various magnetic nanoparticles have been developed. Therefore, the selection of proper magnetic nanoparticles with the desired properties is the first but crucial step for certain bio-applications. For example, ferromagnetic nanoparticles (e.g. Fe nanoparticles) have a large magnetic moment and they can be the best material candidate in magnetic biosensors because they not only produce a better signal but respond to an applied magnetic field readily. On the other hand, iron oxide nanoparticles with super-paramagnetic behavior do an excellent job when used to enhance the signals in magnetic resonance imaging examinations. With the help of iron oxide nanoparticles a sharpened image with detailed information can be achieved because of the change of behavior of nearby bio-molecules by introduced nanoparticles *(Bystrzejewski et al. 2005)*. For many biomedical applications, magnetic nanoparticles presenting super-paramagnetic behavior (no remanence along with a rapidly changing magnetic state) at room temperature are desirable. Biomedical applications are commonly divided into two

major categories: *in vivo* and *in vitro* applications. Consequently, additional restrictions apply on various magnetic nanoparticles for *in vivo* or *in vitro* biomedical applications. It is rather simple for *in vitro* applications of magnetic nanoparticles. The size restriction as well as biocompatibility/toxicity is not so critical for *in vitro* applications, when compared with *in vivo* ones. Therefore, super-paramagnetic composites containing submicron diamagnetic matrixes and super-paramagnetic nanocrystals can be used. Composites with long sedimentation times in the absence of a magnetic field are also acceptable. It was noticed that functionalities may be provided readily for the super-paramagnetic composites because of the diamagnetic matrixes *(Tartaj et al. 2003)*. On the other hand, severe restrictions must be applied for magnetic nanoparticles for *in vivo* biomedical applications. First of all, it is a requisite that the magnetic components should be biocompatible without any toxicity for the bio-systems of interest. This is predominantly determined by the nature of the material (e.g. iron, nickel, cobalt, metal alloy, etc). For instance, cobalt and nickel are highly magnetic materials. However, both of them are rarely used due to their toxic properties and susceptibility to oxidation. Currently, the most commonly employed magnetic nanoparticles in biomedical applications are iron oxides including magnetite (Fe_3O_4), maghemite (γ - Fe_2O_3) and hematite (α-Fe_2O_3). The second requirement for magnetic nanoparticles is their particle sizes. Ultrafine nanoparticles (usually smaller than 100 nm in diameter) have high effective surface area, thus they can be attached to ligand easily. Also the lower sedimentation rate leads to a high stability for colloidal suspensions, and the tissue diffusion can be improved by using nanoparticles in nanometer dimensions. After injection, nanoparticles would be able to remain in the circulation and pass through the capillary systems to reach the targeted organs and tissues without any vessel embolism. Further, the magnetic dipole–dipole interaction among magnetic nanoparticles can be substantially reduced. The third requisite for magnetic nanoparticles is their biocompatible polymer coating which may be done during or after the nanoparticle synthesis. There are several functions of the coating layers: 1) they will prohibit agglomeration of nanoparticles; 2) they prevent structural or elemental changes; 3) unnecessary biodegradation can be stopped; 4) the polymer layer offers a covalent binding or adsorption attachment of drugs to the nanoparticle surface. In summary, for *in vivo* biomedical applications, magnetic nanoparticles must be made of a non-toxic and non-immunogenic material with ultra small particle sizes and high magnetization.

It is no doubt that interdisciplinary research collaboration is badly needed for clinical and biological applications of magnetic nanoparticles *(Berry 2003)*. Research fields involved include chemistry, materials science, cell engineering, clinical tests and other related scientific efforts. In this chapter, an overview of cancer treatment approach as one of biomedical applications of magnetic nanoparticles will be presented

3. Hyperthermia treatment

Another major use of magnetic nanoparticles in therapeutic treatment is hyperthermia treatment for cancers. Gilchrist *et al*. did the experimental investigations for the first time when they heated various tissue samples with γ - Fe_2O_3 of 20–100 nm in diameter by a

1.2MHz magnetic field *(Gilchrist et al. 1957)*. Since then, studies have shown the feasibility of using the hyperthermic effect generated from magnetic nanoparticles by applying a high-frequency AC magnetic field as an alternate therapeutic approach for cancer treatment. Briefly speaking, the hyperthermic effect is generated from the relaxation of magnetic energy of the magnetic nanoparticles which is able to destroy tumor cells effectively *(Levy et al. 2002)*. Hyperthermia is a common cancer therapy in which certain organs or tissues are heated preferentially to temperatures between 41 ◦C and 46 ◦C, artificially induced hyperthermia has been designed to heat malignant cells without destroying the surrounding healthy tissue. When heated to a higher temperature (~56 ◦C), coagulation or carbonization may occur. This 'thermo-ablation' induces a completely different biological response and hence is not considered as hyperthermia. A classical hyperthermia not only causes almost reversible damage to cells and tissues, but also enhances radiation injury of tumor cells *(Jordan et al. 1999)*. For modern clinical hyperthermia trials, moderate temperatures (42–43 ◦C) are normally selected to optimize the thermal homogeneity in the target area. It is true that the heating effect will change the dose-dependent behavior of treated cells. However, the exact mechanism of thermal dose-response in hyperthermia is still unknown. There are great difficulties in identifying the individual cell as the target for hyperthermia. Instead, hyperthermia affects most bio-molecules including proteins and receptor molecules. On the other hand, DNA damage by irradiation has been well understood due to the highly specific interaction. As far as the underlying physics of the heating effect in hyperthermia is concerned, magnetic heating via magnetic nanoparticles essentially is determined by their sizes and magnetic properties *(Mornet et al. 2004)*.

Magnetic nanoparticles can be divided into two major categories: multi-domain and single-domain nanoparticles, which possess different heating effects. Multi-domain nanoparticles usually have larger dimensions and contain several sub-domains with definite magnetization direction for each. When they are exposed to a magnetic field, a phenomenon called 'domain wall displacements' occurs. This is featured by growth of the domain with magnetization direction along the magnetic field axis and shrinkage of the other. Figure 2 above, depicts this irreversible phenomenon. It can be seen that the magnetization curves for increasing and decreasing magnetic field do not coincide, and the area within the hysteresis loop represents the heating energy, named 'hysteresis loss', due to the AC magnetic field. For single-domain nanoparticles, since there is no domain wall, no hysteresis loss occurs leading to no heating. When exposed to an external AC magnetic field, rotation of magnetic moments from super-paramagnetic nanoparticles is assisted by the supplied energy which overcomes the energy barrier. Then these nanoparticles undergo N´eel relaxation in which their moments relax to their equilibrium orientation. Simultaneously, heat is generated during this relaxation by thermal dissipation. The N´eel relaxation time tN is related to the temperature, and can be described as:

$$t_N = t_0 e^{KV/kT} \quad (1)$$

Where $t_0 \approx 10^{-9}$ s, T is the temperature and k is the Boltzmann constant. For both multi- and single-domain nanoparticles, rotational Brownian motion in a carrier also generates heat.

This rotation is caused by the torque exerted on the magnetic moment by the AC magnetic field. The Brown relaxation time t_B is described as:

$$t_B = 3\eta v_B/kT \quad (2)$$

Where η is the viscosity of the carrier, and v_B is the frequency for maximal heating via Brown rotation, corresponding to the hydrodynamic volume of the particle, and it is given by the equation $2\pi v_B t_B = 1$.

The heating capacity of magnetic nanoparticles is expressed by specific absorption rate SAR, also called specific power loss (SPL), both of them have the same physical meaning, which determines the heating ability of magnetic nanoparticles in the presence of magnetic field, and can be defined as the amount of heat generated per unit gram per unit time. SAR values are usually expressed in watts per gram of magnetic material (W/g), also can be expressed in volumetric units (W/m^3).The heat generated per unit volume can be obtained by multiplying the SAR value by the density of the nanoparticles. It has been well documented that the orientation and magnetized domains of magnetic nanoparticles are dependent on their intrinsic features (elemental composition, crystallinity, magneto anisotropy, shape, dimension, etc.) and micro-structural features (impurities, grain boundaries, vacancies, etc). In magnetic hyperthermia treatment, after heat conducts into the area with diseased tissues, the surrounding temperature can be maintained above the therapeutic threshold of 42 ◦C for about half an hour to destroy the cancer. It is of great importance for hyperthermia to minimize the heat effect on healthy cells. Assisted by magnetic nanoparticles, it is possible to heat the specific area while unacceptable coincidental heating of healthy tissue is avoided. Although the hyperthermia treatment for cancer has been demonstrated with therapeutic efficacy in animal models, however, there have been no reports of successful hyperthermia treatment for human patients. The major reasons are the necessities of an adequate amount of magnetic nanoparticles and sufficiently high magnetic field which are not safe for human treatments. To date, laboratory research efforts on hyperthermia treatment for animals have all used magnetic field conditions which are not clinically acceptable. In most instances, hyperthermia treatments with a reduced amount of magnetic nanoparticles and reduced field strength or frequency cannot be effective due to the reduction of heat generated. Simulations suggest a sufficient level with heat deposition rate of $100mWcm^{-3}$ to destroy cancer cells effectively in most circumstances. The practical frequency and strength of the external AC magnetic field are 0.05–1.2MHz and 0–15 kAm^{-1}, respectively. On the other hand, sufficient magnetic materials are needed to enrich around the cancer tissues to generate enough heat for hyperthermia treatment. Direct injection of ferrofluid into the tumor tissues is able to introduce a large amount of magnetic materials for heat generation. Antibody targeting and intravascular administration offer better preference heating, but the problem here is the small quantity. It is estimated that about 5–10 mg of magnetic material concentrated in each cm^3 of tumor tissues is able to generate enough heat for tumor cell destruction in human bodies. Magnetite (Fe_3O_4) and maghemite (γ -Fe_2O_3) nanoparticles are two common types used in hyperthermia treatments owing to their appropriate magnetic properties and their excellent biocompatibilities. Several examples will be given here.

The history of using magnetic particles for selective heating of the tumors started in 1957 when Gilchrist et al used particles of a few mm in size for inductive heating of lymph nodes in dogs (*Gilchrist et al., 1957)*. More than 20 years later, Gordon et al used a magnetic fluid ('dextran-magnetites' with a core size of up to ~ 6 nm) for inducing hyperthermia *(Jordon et al., 1979)*. Injection of micro-scaled ferromagnetic particles into renal carcinomas of rabbits and subsequent heating was reported by Rand and co-workers *(Rand et al., 1981)*. Magnetic nanoparticles used in a different approach termed as ferromagnetic embolization. In this technique, the MNPs were injected into the main feeding artery of the tumor; this injection resulted in aggregates of MNPs which in turn embolized the feeding artery and hence necrosis of the tumor cells. This technique seems to be especially well suited for the treatment of hepatic malignancies due to the differences in blood supply between hepatic tumor cells and normal liver parenchyma *(Archer et al., 1990)*. Direct injection of dextran-coated magnetite NPs with a core size of ~ 3 nm into tumors was first reported in 1997 *(Jordan et al., 1997)*. Other groups in Japan developed "magnetic cationic liposomes" (MCLs) with improved adsorption and accumulation properties within tumors and demonstrated the efficacy of their technique in several animal tumor models: rat glioma *(Le et al., 2001)*. Hilger et al injected colloidal suspensions of coated MNPs (particle sizes of ~10 nm and 200 nm) into human carcinomas implanted into mice *(Hilger et al., 2002)*. Ohno et al inserted stick-type carboxymethyl cellulose magnetite containing NPs into gliomas and described as a three-fold prolongation of survival time *(Ohno et al., 2002)*. Moroz and co-workers concluded from their data that for a given tumor iron concentration, larger tumors heat at a greater rate than small tumors due to the poorer tissue cooling and better heat conduction in the necrotic regions of large tumors *(Moroz et al., 2002)*. Tanaka et al used MCLs in melanoma in combination with immunotherapy *(Tanaka et al., 2005)* and used for prostate cancer treatment *(Kawai et al., 2005)*. Yan *et al*. demonstrated the use of Fe_2O_3 nanoparticles combined with magnetic fluid for hyperthermia treatment on human hepatocarcinoma SMMC-7721 cells *in vitro* and xenograft liver cancer in nude mice (2005). Their experiments verified the significantly inhibitory effect of magnetic ferrofluid in weight and volume on xenograft liver cancer. After infiltrating magnetic ferrofluid into the target tissues, a time-varied magnetic field was applied and its energy was transformed to heat energy by the magnetic nanoparticles resulting in a temperature rise to 42–45 ◦C. This generated heat is able to kill malignant tumor cells without injuring the normal cells nearby. The growth and apoptosis of SMMC-7721 cells treated with the ferrofluids containing Fe_2O_3 nanoparticles at various concentrations (2, 4, 6 and 8 mg/ml) were examined by MTT, flow cytometry (FCM) and transmission electron microscopy (TEM) after 30–60 minute treatments. It was observed that Fe_2O_3 nanoparticles-based ferrofluid could significantly inhibit the proliferation and increase the ratio of apoptosis of SMMC-7721 cells. These dose-dependent inhibitions were 26.5 %, 33.53 %, 54.4 %, 81.2 %, and 30.26 %, 38.65 %, 50.28 %, 69.33 %, for inhibitory rate and apoptosis rate, respectively. It was also observed from animal experiments that the tumors became smaller and smaller as the dosage of magnetic ferrofluid increased. The weight and volume inhibitory ratios were 42.10 %, 66.34 %, 78.5 %, 91.46 %, and 58.77 %, 80.44 %, 93.40 %, 98.30 %, respectively. In a comparison of the control and experimental groups, each group exhibited significant difference. According to histological examination,

many brown uniform spots are located at the stroma in the margin of the tumors, which are identified as iron oxide nanoparticles. Although interstitial hyperthermia following direct injection of nanoparticles has been proven successful in many animal models, nevertheless only one of these approaches has been successfully translated from research to clinical stage for prostate cancer treatment either by iron oxide against RF ,this clinical studies were performed by Johannsen 2005.

Fumiko et al 2004 developed magnetite cationic liposomes (MCLs) and applied them to local hyperthermia as a mediator. MCLs have a positive charge and generate heat under an alternating magnetic field (AMF) by hysteresis loss. In this study, the effect of hyperthermia using MCLs was examined in an in vivo study of hamster osteosarcoma. In this study, three-week-old Syrian female hamsters were purchased from Japan SLC, Inc., Shizuoka, Japan, and used for the animal study. After that MCLs were injected into the osteosarcoma and then subjected to an AMF. The results revealed that, the tumor was heated at over 42°C, but other normal tissues were not heated as much. Complete regression was observed in 100% of the treated group hamsters, whereas no regression was observed in the control group hamsters. At day 12, the average tumor volume of the treated hamsters was about 1/1000 of that of the control hamsters. In the treated hamsters, no regrowth of osteosarcomas was observed over a period of 3 months after the complete regression. These results suggest that this treatment is effective for osteosarcoma.

One of recent and novel study was applied by El Sherbini et al (2011). The aim of this experimental study is to evaluate the effect of magnetic resonance on magnetic nanoparticles, this *in -vivo* experiments in which hyperthermia is induced in female Swiss albino mice weighing 20.0 to 29.2g median, 26.3g implanted with subcutaneous *Ehrlich* carcinoma cells under magnetic resonance imaging. The strategy of this study was based on preparation, characterization of super-paramagnetic magnetic iron oxides nanoparticles and evaluation of magnetic resonance hyperthermia (MRH) technique in presence of super-paramagnetic nanoparticles and an alternating magnetic field (AMF).

Preparation of tumors bearing mice and iron oxide magnetic nanoparticles followed the method described by Elsherbini et al (2011). The prepared SPIO nanoparticles were suspended in glycerin medium to increase the stability especially *in vivo* conditions. The prepared suspension was stable for several months due to the high viscosity of glycerin. The influence of the SPIO nanoparticles concentration on the total amount of specific heat energy dose (SED) was studied in a preliminary study. The mean values of the total cumulative specific energy dose were monitored for different concentrations of SPIO nanoparticles in the tumors. The mean values reported of SED Jgm^{-1} were [282.1±13.8 for (200μg), 462.7±10.0 for (400μg), 663.7±13.0 for (600μg), 864.1±16.6 for (800μg) and 1087 ±18 for (10^3μg)] as shown in figure (3). The quantitative analysis revealed that, the SED values were directly proportional to the concentrations of the injected nanoparticles inside the tumors.

The results of heat deposition rate HDR inside the tumor revealed that, the mean values of HDR were [0.157 for (200μg), 0.259 for (400μg), and 0.367 for (600μg), 0.478 for (800μg) and 0.604 for (10^3μg)] as shown in figure (4). These values varied considerably between the

different concentrations of SPIO nanoparticles with highly significant p value p <.007. The temperature changes were recorded in the intra-tumoural SPIO nanoparticles accumulation. The results revealed that the maximum temperatures achieved were [40.11±1.52°C for (200μg), 42.36±1.54°C for (400μg), 44.43±2.0°C for (600μg), 46.8±1.5°C for (800μg) and 48.6±1.0 °C for (10^3μg)] as shown in figure (5).The time taken to maximum temperature TMT was recorded as [40±2.5 min for 200&400μg, 30±2.0 min for 600μg, 25±5.0 min for 800μg and 20± 5.0 min for 10^3μg] as shown in figure (6). The statistical analysis revealed that the TMT values were inversely proportional to the concentrations of the injected nanoparticles inside the tumors. *In vivo* experiments for magnetic resonance hyperthermia demonstrated that the use of SPIO nanoparticles combined with magnetic resonance for hyperthermia treatment on Ehrlich carcinoma. The experiments revealed that after treatment sessions, magnetic resonance images verified degree of apoptotic cells presented by dark signal intensity in the center of the tumor in all mice on T1 weighted images; the centers of the lesions were asymmetrical and non-homogenous when compared to magnetic resonance images before treatment, as well as the images showed variations in signal intensity in the abdominal regions attributed to the distribution of the SPIO nanoparticles over the treatment sessions as shown in figure (7). As well as the experiments verified the significantly inhibitory effect of SPIO nanoparticles in volume on Ehrlich tumor. Significant volume differences between mice in all groups under experiments are shown in figure (8). It worth mentioning that, histopathology examination was further used to confirm MR results.

Plasmonic photo-thermal therapy (PPTT).Gold nanoshells belong to a prospective class of optical adjustable nanoparticles with a dielectric silica core encased in a thin metallic gold shell (Hirsch, et al 2006). The absorption cross-section of a solid nanoshell is high enough to provide a competitive nanoparticle technology with application of indocyanine green dye, a typical photothermal sensitizer used in laser cancer therapy (Gupta, et al 2007).

On the other hand, there are several *in vitro* experiments concerning application of gold nanoparticles and core shell NPs to PPTT of cancer cells, while number of *in vivo* studies is quite limited (Loo, et al, 2005). The first account of the use of gold nanoparticles in hyper-thermal therapy was published in 2003. Halas et al used gold -on-silica nanoshells to treat breast carcinoma cells using the HER2 antibody *(Hirsch et al., 2003)*. Another study using pulsed laser and gold nanospheres was performed in 2003 by Lin and co-workers for selective and highly localized photothermolysis of targeted lymphocytes cells. Lymphocytes incubated with gold nanospheres conjugated to anti-bodies were exposed to nanosecond laser pulses (Q-switched Nd: YAG laser, 565 nm wavelength, 20 ns duration) .The results showed that 100 laser pulses at an energy of 0.5 J/cm^2 were sufficient to induce cell death. While adjacent cells just a few micrometers away without nanoparticles remained viable *(Pitsillides et al., 2003)*. In the same year, Zharov et al performed similar studies on the photo-thermal destruction of K562 cancer cells. They further detected the laser induced- bubbles and studied their dynamics during the treatment using a pump–probe photo thermal imaging technique *(Zharov et al., 2003)*. O'Neal et al 2004 reported *in vivo* impressive results by showing selective photo-thermal ablation in mice using near infrared-absorbing NPs *(O'Neal et al., 2004)*. Another *in vivo study was applied on* a murine model using NIR light against gold nanoshells (*Loo et al., 2004*).

In a study by El- Sayed and co-workers conjugated gold nanoparticles of approximately 40 nm to anti-epithelial growth factors receptors (EGFR) antibodies and targeted to types of human head and neck cancer cells, the nanoparticles induce cancer cell damage at 19 W/cm^2 after the irradiation with argon Ar^+ laser at 514 nm for 4 min, while healthy cells do not show the loss of cell viability under the same treatment *(El Sayed et al., 2005)*.

Huang et al also described the photo-thermal destruction of cancer cells using bio-functionalized gold nanorods. The nanorods were conjugated to anti- EGFR (specific antibody to the malignant cell types used), and then incubated with a non-malignant epithelial cell line (HaCat), as well as two malignant oral epithelial cell lines (HOC313 clone8 and HSC3). Following laser irradiation, the results revealed that the malignant cells were destroyed at about half the laser fluence needed to kill the nonmalignant cells. The efficient destruction of the malignant cells was evidently due to the preferential attachment of the anti-EGFR-gold nanorod conjugates to the over-expressed EGFR on the surface of the malignant cell *(Huang et al., 2006)*.

In 2006, El-Sayed and co-workers conjugated gold nanorods to anti-EGFR antibodies specifically bind to the head and neck cancer cells, these labeled cells subjected to laser irradiation (Ti: Sapphire laser, CW at 800 nm) which was maximally overlapped with the surface plasmonic resonance absorption band of the nanorods. Under laser exposure for 4 min, it was found that the cancer cells required half the laser energy (10 W/cm^2) to be photo-thermally damaged as compared to the normal cells (20 W/cm^2) *(El Sayed et al., 2006)*.

In 2007, Huff and co-workers conjugated folate ligands with oligo-ethylene-glycol onto gold nanorods by *in situ* dithio-carbamate formation; the folate conjugated gold nanorods were selectively bound to KB cancer cells (a tumor cell line derived from oral epithelium) which led to photo-thermal damage on cell membranes following laser irradiation *(Huff et al., 2007)*. Another study from the same group showed that under laser irradiation membrane blebbing occurred due to the influx of calcium ion Ca^{2+} into the cells *(Tong et al., 2007)*.

Attempts using gold nanocages for PPPT have also been made recently. In the *in vitro* studies by Li and co-workers conjugated gold nanocages of approximately 30 nm to anti-EGFR to target A431 cells. At laser energy density of 40 W/cm^2, almost all immunonanocage treated cells were damaged *(Li et al., 2008)*. Other *in vitro* studies by Xiaohug and co-workers using gold nanocages of approximately 45 nm conjugated to HER-2 and near infrared femtosecond Ti: Sapphire pulsed laser to treat Sk-BR-3 breast cancer cells *(Xiaohua et al., 2010)*.

Paul and Tuan reported the application of liposome-encapsulated gold nanoshells for in vitro photo-induced hyperthermia in human mammary carcinoma cells. In addition to evaluating their effects in vitro, the authors compared the application liposome-encapsulated gold nanoshells and free-standing gold nanoshells for NanoPhotoTherapy (NPT). NPT-induced hyperthermia was performed using a 785-nm near-infrared light from a diode laser and the in vitro effects were evaluated using nucleic acid molecular probes by fluorescence microscopy. Additionally, they monitored the effectiveness of NPT by

detecting apoptosis via capase-9 activity. The experiments clearly showed that liposomal delivery enhanced the intracellular bioavailability of gold nanoshells and thus is able to induce a higher degree of cell death more effectively than free-standing gold nanoshells.

Single-walled carbon nanotubes (SWNTs) have a high optical absorbance in the near-infrared (NIR) region. In this special optical window, biological systems are known to be highly transparent. The optical properties of SWNTs provide an opportunity for selective photo thermal therapy for cancer treatment. Specifically, SWNTs with a uniform size about (0.81 nm) and a narrow absorption peak at 980 nm are ideal candidates for such a novel approach. In a study by Feifan et al, SWNTs are conjugated to folate, which can bind specifically to the surface of the folate receptor tumor markers. Folate- SWNT (FA-SWNT) targeted tumor cells were irradiated by a 980 nm laser. Results in *vitro* and *in vivo* experiments revealed that FA-SWNT effectively enhanced the photo thermal destruction on tumor cells and noticeably spared the photo thermal destruction for non targeted normal cells. Thus, SWNTs, combined with suitable tumor markers, can be used as novel nanomaterials for selective photo thermal therapy for cancer treatment. The authors used the mammary tumor model with EMT6 cells in the female Balb/c mice to investigate the *in vivo* effects of FA-SWNT. The mouse tumors with or without FA-SWNT were treated by the 980-nm laser. To determine the effects of NIR optical excitation of SWNTs inside tumors, the authors measured the temperature on the tumor surface during the irradiation by the 980-nm laser with an infrared thermal camera. In one experimental mouse, irradiation of tumors with a power density of 1 W/cm2 with FA-SWNT (1 mg/kg) for 5 min caused a surface temperature elevation of 63 °C. Without FASWNT, the tumor irradiated at the same light dose caused a surface temperature elevation of 54 °C. Experiments with other animals yielded similar results. These findings clearly show that FA-SWNT could effectively enhance the tumor photo thermal therapy.

Kim et al achieved close to 90% cancer cell destruction in vitro using FeNi@Aumagnetic-vortex microdiscs (MDs), on the application of only a few tens of hertz AMF for just 10min. This confirms that operation of MFH at lower frequencies is possible and for effective heat generation can be achieved using core–shell type of structures. Likewise, in yet another demonstration, a gold coating of approximately 0.4 to 0.5 nm thickness around SPIONs resulted in a four- to five-fold increase in the amount of heat released (the highest value of 976W/g in ethanol at 430 Hz frequency) in comparison with SPIONs on application of low frequency oscillating magnetic fields (44–430 Hz). This study was done by Mohamed et al 2010. In addition, the SPIONs@Au were found to be not particularly cytotoxic to mammalian cells. (MCF-7 breast carcinoma cells and H9c2 cardiomyoblasts) in *in vitro* studies were done by Pollert et al 2010. When similar heating experiments were carried out using stable water suspensions of La0.75Sr0.25MnO3 cores covered by silica (conc. of Mn=3.39 mg/ml), highest SAR of 130 W/g Mn at 37 °C was reached for the applied amplitude and frequency of 8.7 kAm−1, 480 kHz respectively.

In this context, a study was done by Elsherbini and co-workers, 2011. The group evaluated two different approaches in the nanotechnology era for inducing hyperthermia in

subcutaneous Ehrlich carcinoma cells. The first called Optical Resonance Hyperthermia (ORH) technique in presence of gold nanospheres and green diode laser, as shown in fig (9). While the second technique called Magneto-Optical Resonance Hyperthermia (MORH), in presence of gold-iron oxide core shell nanoparticles with green, near infra-red diode laser, and magnetic field, as shown in fig (10). This approach was performed under magnetic resonance imaging guidance. The results revealed that, all mice treated by the first technique, the tumors were still as the same as before the treatments, as well as the rate of tumors growth were very slow if compared with the control mice. In contrast more than 50% of the mice treated with the second technique revealed a complete disappearance of the tumor, as shown in figure (11). So the study have demonstrated that a pair of synthetic nanospheres can work together more effectively for inducing hyperthermia than individual nanospheres, whereby more than .So, this simple, non-invasive method shows great promise as a treatment technique for clinical setting.

There are two main advantages of the plasmonic photothermal therapy technique. Firstly, there is the benefit of photostability compared with the photosensitizer dyes used in photodynamic therapy, which suffer from photobleaching as well as diffusion under laser irradiation. Secondly, there is the advantage of absorption and scattering cross-sections of gold nanoparticles, which are significantly superior to the absorbing dyes conventionally used in biological systems. Mie theory estimates that the optical cross-sections of gold nanospheres are typically four to five orders of magnitude higher than those of conventional dyes.

In spite of much progress having been made using the plasmonic photothermal therapy technique for cancer treatment in a laboratory setting, there are still many factors which must be taken into account before this method may be taken to a clinical setting, and they need to be studied further. First of all, the distribution of the elevated temperature under plasmonic photothermal therapy treatment is related to absorption of light by nanospheres acting as point wise local heat sources and by thermal diffusion over surrounding tissues. At the practical level, plasmonic photothermal therapy needs to provide an appropriate temperature increment, ΔT, gold nanosphere concentration, laser power density, duration of laser exposure, optimization of absorption and scattering cross-sections of nanospheres, as well as penetration of the laser light into the area of interest. It should be noted that the biological effects have a nonlinear dependence on changes in particle concentration and laser power density, which is defined by the type of tissue and thermoregulation ability of the living organism.

Although interstitial hyperthermia following direct injection of nanoparticles has been proven successful in many animal models, nevertheless only one of these approaches has been successfully translated from research to clinical stage for prostate cancer treatment either by iron oxide against RF ,this clinical studies were performed by Johannsen 2005. The aim of this pilot study was to evaluate whether the technique of magnetic fluid hyperthermia can be used for minimally invasive treatment of prostate cancer. This paper presents the first clinical application of interstitial hyperthermia using magnetic

nanoparticles in locally recurrent prostate cancer. Treatment planning was carried out using computerized tomography (CT) of the prostate. Based on the individual anatomy of the prostate and the estimated specific absorption rate (SAR) of magnetic fluids in prostatic tissue, the number and position of magnetic fluid depots required for sufficient heat deposition was calculated while rectum and urethra were spared. Nanoparticle suspensions were injected transperineally into the prostate under transrectal ultrasound and flouroscopy guidance. Treatments were delivered in the first magnetic field applicator for use in humans, using an alternating current magnetic field with a frequency of 100 kHz and variable field strength (0–18 kAm^{-1}). Invasive thermometry of the prostate was carried out in the first and last of six weekly hyperthermia sessions of 60 min duration. CT-scans of the prostate were repeated following the first and last hyperthermia treatment to document magnetic nanoparticle distribution and the position of the thermometry probes in the prostate. Nanoparticles were retained in the prostate during the treatment interval of 6 weeks. Using appropriate software (AMIRA), a non-invasive estimation of temperature values in the prostate, based on intra-tumoural distribution of magnetic nanoparticles, can be performed and correlated with invasively measured intra-prostatic temperatures. Using a specially designed cooling device, treatment was well tolerated without anesthesia. In the first patient treated, maximum and minimum intraprostatic temperatures measured at field strength of 4.0–5.0 kAm^{-1} were 48.5^0C and 40.0^0C during the 1st treatment and 42.5^0C and 39.4^0C during the 6th treatment, respectively. These first clinical experiences prompted us to initiate a phase I study to evaluate feasibility, toxicity and quality of life during hyperthermia using magnetic nanoparticles in patients with biopsy-proven local recurrence of prostate cancer following radiotherapy with curative intent. To the authors' knowledge, this is the first report on clinical application of interstitial hyperthermia using magnetic nanoparticles in the treatment of human cancer.

Akihiko et al have developed a novel hyperthermic treatment modality using magnetic materials for metastatic bone tumors. The purpose of this study is to show the results of novel hyperthermia for metastatic bone tumors. This novel hyperthermic treatment modality was used for 15 patients with 16 metastatic bone lesions. In seven lesions, after curettage of the metastatic lesion followed by reinforcement with a metal intra-medullary nail or plate, calcium phosphate cement (CPC) containing powdery Fe_3O_4 was implanted into the cavity. In one lesion, prosthetic reconstruction was then performed after an intralesional tumor excision. For the remaining eight lesions, metal intra-medullary nails were inserted into the affected bone. Hyperthermic therapy was started at 1 week postoperatively. To comparatively evaluate the radiographic results of patients who underwent hyperthermia (HT group), the authers also assessed eight patients who received a palliative operation without either radiotherapy or hyperthermia (Op group), and 22 patients who received operation in combination with postoperative radiotherapy (Op + RT group). In HT group, all patients had an acceptable limb function with pain relief without any complications. On radiographs, 87, 38, and 91% were, respectively, considered to demonstrate an effective treatment outcome in HT group, Op group, and Op + RT group. The patients in HT group showed a statistically better radiographic outcome than the

patients in Op group (P = 0.0042). But when compared between HT group and Op + RT group, there were no significant difference (P = 0.412). This first series of clinical hyperthermia using magnetic materials achieved good local control of metastatic bone lesion.

Study by Manfred et al 2007, or by using laser against gold nanoparticles, for instance Yusheng et al 2009 used core shells (silica as a core with a diameter 110nm and an outer gold shell with thickness 15 nm) to mediate laser surgery stimulation for prostate cancer treatment. The goal of this paper is to present an integrated computer model using a so-called nested-block optimization algorithm to simulate laser surgery and provides transient temperature field predictions. In particular, this algorithm aims to capture changes in optical and thermal properties due to nanoshell inclusion and tissue property variation during laser surgery. Numerical results show that this model is able to characterize variation of tissue properties for laser surgical procedures and predict transient temperature field comparable to that measured by in vivo magnetic resonance temperature imaging (MRTI) techniques. Note that the computational approach presented in the study is quite general and can be applied to other types of nanoparticle inclusions.

In conclusion, this is a brief review on different approaches for inducing hyperthermia cancer treatment relevant to nanomedicine

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