A Review Paper on Iron Oxide Nanoparticle Based Strategies in Cancer Treatment

By

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School of Pharmacy

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Declaration

It is hereby declared that –

1. The thesis submitted is my/our own original work while completing a degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I/ We have acknowledged all main sources of help.

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Approval

The project titled “A Review Paper on Iron Oxide Nanoparticle Based Strategies in Cancer Treatment” submitted by Somaiya Akter Bithy (18346062) on Spring2022 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons) in November, 2022.

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Ethics Statement

This study does not involve any animal or human trial.

Abstract

The advanced approach of magnetic iron oxide nanoparticles (IONs) offers new opportunities in the field of diagnosing life-threatening diseases including cancer treatment. Due to their superior magnetic anisotropy, irreversible ability of high and low field magnetization, and superparamagnetism, they display the special potential to respond to therapeutic doses (in magnetic hyperthermia and targeted drug delivery). This review focuses on the current progress of the IONs application as magnetic therapeutic agents along with the synthesis methods and surface modification to enhance efficacy of the particles. The findings include the use of these nanoparticles for cancer treatment in the form of contrast agent, drug carriers, and through cell tracking with the assistance of MRI. Lastly, some emerging problems associated with IONs toxicity and the necessary steps that should be established to overcome them are mentioned briefly as well.

Keywords: cancer therapy; magnetic iron oxide nanoparticles; biomedical application; surface functional strategy; hyperthermia; MRI.

Dedication

Dedicated to my mother, without whom I would not be where I am today.

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To begin with, I would like to convey my gratitude to almighty Allah for guiding me, giving me the strength, and power of mind to complete this project.

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Table of Contents

List of Tables

List of Figure

List of Acronyms

Chapter 01

Introduction

1.1. Background

Cancer is a leading cause of death worldwide, causing nearly 10 million deaths in 2020, or about one death in six (WHO, 2022). It is a genetic disease which occurs due to the alterations of genes that are supposed to control the functions of cells, namely their division, maturation, and growth. Cancer cells exhibit a significant loss of growth control because of cumulated decrease in various cell regulatory functions that is manifested across many important features of cell activity that usually distinguish cancer cells from their healthy equivalents (Cooper, 2000). A healthy cell transforms into a tumor cell when one or several mutations occur in its DNA, also known as neoplastic transformation. These genetic changes are either inherited or acquired. Acquired genetic changes can occur because of certain environmental exposures, e.g., radiation (UV, X-rays, gamma rays), viruses (hepatitis B, hepatitis C), chemical carcinogens (tobacco products, asbestos, azo dyes). Genetic changes can also occur due to errors during cell division (NIH, 2021). For instance, woman who inherits one altered copy of either the tumor suppressor genes BRCA1 or BRCA2 have a higher risk of developing ovarian cancer and breast cancer because the inactivation of a single copy of these genes due to mutation during cell division leaves breast or ovarian cells exposed to cancer as their ability to repair DNA damage is decreased (Lee & Muller, 2010).

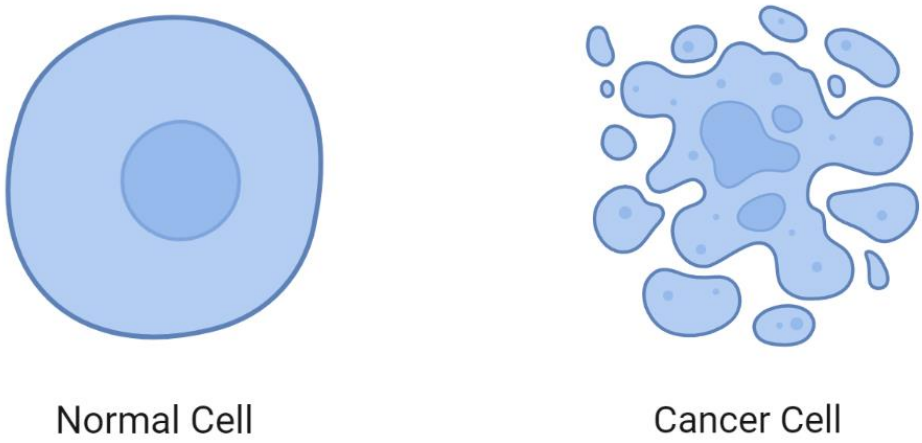

Figure 1: Normal cell vs cancer cell

In the male population, the most common types of cancer include lung, stomach, liver, prostate, colorectal cancer, whereas breast, lung, colorectal, cervical, thyroid cancer are the most common among the female population (WHO, 2022).

Tumors can be classified on the basis of their origin, invasivity, their tendency to spread to different parts of the body, and their ability of metastasis. Benign tumors are not much harmful because they cannot invade or spread into other parts of the body. On the other hand, malignant tumors are considered more fatal due to their ability to penetrate the bloodstream or lymphatic system resulting in secondary tumor development in different parts of the body (Chambers et al, 2002).

Depending on the classification of cancer and how far along the progression of tumor is, there are different types of cancer therapy available. Some patients may need only one kind of cancer therapy but most patients require a combination of therapies to fully recover. Chemotherapy is one of the standard treatment methods during which drugs containing powerful chemicals are used to inhibit cellular division and growth by interfering with DNA synthesis of cancer cells causing cell death. However, problems associated with this method arise serious concern

(DeVita & Chu, 2008). One of the fundamental issues regarding chemotherapy is the development of cellular drug resistance. For example, some neoplastic cells, melanoma, are inherently resistant to most anticancer drugs without any prior exposure to cytotoxic agents. Other resistance develops in response to exposure to a given anti-cancer agent by developing mutations, particularly after prolonged administration of sub-optimal drug doses. Another fatal adverse effect is toxicity as this therapy kills cells non-specifically which means it affects normal cells along with rapidly proliferating cancer cells, e.g., hair follicles, bone marrow, cells of the buccal mucosa, gastrointestinal mucosa etc. Furthermore, Myelosuppression is common to many chemotherapeutic agents which increases the risk of infections. Other adverse reactions include bladder toxicity, cardiotoxicity, and pulmonary fibrosis (Chivere et al., 2020).

Another type of cancer treatment is radiotherapy where elevated frequency of radiation is used to destroy or shrink the tumorous cells but it is also responsible for damaging healthy cells (Sebag-Montefiore et al., 2009) and surgery which is done when the tumor is in solid form, is found in only one part of the body, and easy to remove without affecting any vital organ. The surgeon performs the surgery through cutting into the body and removing the tumor along with some nearby healthy cells to ensure that the entire tumor is removed (*Cancer surgery: Physically removing cancer*, 2020).

Over the last decade, the concept of cancer treatment has gained a lot of attention because of its severe effects on human life span. The principle of cancer therapy is to destroy only the cancer cells with minimal destruction to healthy cells. However, it is not easy to distinguish the cancer cells from healthy cells, thus the already existing treatments, e.g., chemotherapy, tumor-selective radiation therapy etc. are less effective and associated with many adverse effects (Maenosono & Saita, 2006). Therefore, an improved strategy should be developed

which can decrease the therapeutic doses and deliver therapeutic drugs into the tumor cells directly under different conditions (Senapati, 2018).

1.2. Nanoparticles

The implementation of nanoparticles in the drug delivery system has yielded many probabilities to address and tackle some of the deadly diseases including cancer. The obstacles associated with the conventional cancer therapy include non-specificity that results in off-target toxicity which destroys healthy cells, poor circulation time causes reduced efficacy, and drug resistance leads to decreased intra-tumoral retention. Therefore, nanoparticles are used in targeted drug delivery to deliver the drug to the targeted site, to improve the uptake of less soluble drug, and to enhance bioavailability of drug (Dean, Wang, & Hua, 2015).

Nanoparticles differ in size but normally range from 100 to 500 nm. By controlling the size, material used, surface properties, the nanoparticles can be evolved into smart techniques, containing therapeutic and imaging agents, stealth properties etc. Moreover, these techniques can deliver drugs to targeted tissues and give sustained release therapy. This targeted and controlled drug delivery reduces the drug borne toxicity and improves patient's compliance due to less frequent dosing. Nanoparticles have been used successfully for cancer drug delivery since 1995 (Rizvi & Saleh, 2018).

Magnetic nanoparticle (MNP) has been actively investigated as the succeeding targeted drug delivery particle for more than 30 years due to their ability to function at the molecular and cellular level of biological reactions and distinctive physical properties (Xu et al., 2009). Transferring a drug to the midpoint of the disease directly under different environments and treating it effectively without any adverse effects on the body is the main goal of targeted drug delivery and therapy (Chomoucka et al., 2010).

As mentioned before, non-specificity is the main drawback of almost all chemotherapeutic approaches. Generally, therapeutic drugs are cytotoxic and administered intravenously resulting in systemic distribution. The non-specific characteristic of this method leads to the common aftereffects of chemotherapy because the cytotoxic drug attacks not only the targeted tumor cells but also the non-targeted healthy cells (Gaihre et al., 2009). To diminish this downside, MNPs can be applied to treat cancer in 3 different ways. Firstly, specific antibodies are conjugated to the MNPs, so that they can selectively bind to targeted receptors and inhibit tumor cell growth. Secondly, targeted MNPs are used for hyperthermia for cancer therapy. Lastly, drugs can be loaded onto the MNPs for targeted delivery (Chomoucka et al., 2010). The targeted therapy of anti-cancer is a great substitute to traditional chemotherapy where these agents are adsorbed on the surface of MNPs. In this method, with the help of an external magnet, the particles are loaded into the drug and are concentrated at the targeted site. Then the drugs are delivered to the designed site (Sivudu et al., 2009). Magnetic particles which are smaller than 4 μm are excreted by the cells of the reticuloendothelial system (RES), primarily in the spleen (3–10%) and liver (60–90%). On the other hand, particles which are bigger than 200 nm are mostly excreted to the spleen, whereas liver cells phagocytose particles up to 100nm. At large, the larger the particle size, the shorter their period of plasma half-life (Abdalla et al., 2010).

1.3. Magnetic Iron Oxide (IO) Nanoparticles

Magnetic iron oxides are considered as major nanomaterials for biomedical applications in vivo and in vitro because of their large surface area, long blood retention time, enhanced permeability, stability, biocompatibility, biodegradability, precise targeting, and low toxicity. Moreover, they can be modified by manipulation to provide a large number of functional groups for cross-linking to tumor-targeting ligands, e.g., peptides, monoclonal antibodies, and

small molecules for molecular and cellular imaging, cancer treatment, and integrated nanodevices for detecting the cancer cell, screening, and delivery of therapeutic agents (Cheetham et al., 2016).

Chapter 02

Methodology

The review was done by following a secondary research method which involved compiling existing data from a variety of sources including government statistics, organizational bodies, the internet etc. Methodical literature review was done to obtain all the information from various credible sources like research papers, news articles, academic published articles, peer reviewed journals, online scholarly databases etc. Additionally, several databases were searched extensively for this study such as journal database, newspaper database, library catalog, professional website. and many more. Data were also collected from PubMed, a website that gives permission to make use of biomedical journal abstracts and citations primarily indexed by Medline without any charge. Articles from renowned journals such as Journal of Cancer Research and Clinical Oncology, Elsevier, Wiley online library etc. were also evaluated for this review study. Furthermore, the cancer website e.g., American Cancer Society, American Society of Clinical Oncology (ASCO), US National Cancer Institute (NCI), government websites e.g., Comprehensive Cancer Information, National Institutes of Health (NIH), MedlinePlus, and international websites e.g., World Health Organization (WHO), International Agency for Research on Cancer (IARC) were used to retrieve potential data for completing the review. At last, the information was combined to better understand the topic and express it precisely in writing.

Chapter 03

Synthesis, Properties, and Surface Coating of Iron Oxide Magnetic Nanoparticles

3.1. Synthesis of iron oxide nanoparticles

Many processes have been developed for synthesizing magnetic NPs with appropriate surface chemistry such as physical, chemical, and biological. Recently, iron is the most transition metal in the Earth's crust, so it is considered as the backbone of modern infrastructure. However, iron oxides are not used as much compared to other group elements like cobalt, nickel, gold, and platinum). There are about 16 identified iron oxides where iron is chemically combined oxygen to form iron oxide compounds. Naturally, iron (III) oxide can be found in the form of rust (Zia et al., 2016). Therefore, iron oxides are commonly used as they are not expensive and play a significant part in many biological approaches (Laurent et al., 2008). Magnetite (Fe3O4), maghemite (g-Fe2O3), and hematite (α-Fe2O3) are the three most common forms of iron oxides found in nature. NPs which are made of ferromagnetic materials with size of <10-20 nm display an incomparable nature of magnetism, i.e., superparamagnetism which is responsible for low toxicity, superparamagnetic properties, such as surface area and volume ratio, and simple separation methodology, thus capable of biomedical applications for protein immobilization, e.g., diagnostic magnetic resonance imaging (MRI), thermal therapy, and drug delivery (Nurdin et al., 2016). IONs can generate magnetic resonance spontaneously by moving along the field of attraction or involving the external magnetic field, or through self-heating which are greatly affected by size, shape, crystallization, synthetic methods, and quality of the IONs (Xu et al., 2014).

IONs can be synthesized using mechanochemical methods which include combustion, laser ablation arc discharge, pyrolysis, electrodeposition etc. and chemical methods which include coprecipitation, hydrothermal, sol–gel synthesis, reverse micelle template-assisted synthesis etc. (Zia et al., 2016). The most efficient synthesis methods are hydrothermal synthesis, co-precipitation, microemulsion, thermal decomposition, and sonochemical synthesis which ensures the development of monodispersed IONs with controlled size and shape, stability, and biocompatibility (Daou et al., 2006). Co-precipitation and thermal decomposition are the most commonly used techniques.

3.1.1. Co-precipitation synthesis

The most convenient method to obtain Fe3O4 or ɤ-Fe2O3 is co-precipitation which is a chemical preparation method and is performed by adding ferrous and ferric salts together in the presence of strong solutions of base (Mascolo et al., 2013). This reaction is done in the presence of an inert gas (N2 or Ar) in an oxygen-free environment using degassed solutions to prevent out of control oxidation of Fe2+ to Fe3+ (Bandhu et al., 2009). Mostly, the particles are covered with organic or inorganic coating to prevent oxidation. On the other hand, bubbling nitrogen gas prevents oxidation and reduces the size of the particles (Maity & Agrawal, 2007). In this process, using alkaline solutions (sodium hydroxide, potassium hydroxide, or ammonium hydroxide), Fe2+ and Fe3+ ions are precipitated. The size, shape, and composition of the IONs depends on the type and amount of salt used, i.e., the ratio of Fe2+ and Fe3+, mixing methods (Mizukoshi et al., 2009), pH value, reaction temperature, ionic strength of the media, digestion time, dropping speed of basic solution, stirring rate, presence or absence of a magnetic field on particle size (Vereda et al., 2007), and some other reaction parameters.

In addition, some of the co-precipitation synthesizing methods are carried out in the presence of polymers, such as dextran or polyvinyl alcohol (PVA) to avoid either oxidation or agglomeration or both. (Pardoe et al., 2001).

Co-precipitation technique produces water-soluble magnetic nanoparticles and has comparatively low production expense and relatively high yield to other synthesis methods. Moreover, this chemical method is simple and efficient and in this technique, the size, shape, and composition of the NPs can be adjusted as well. However, this method leads to less control over hydrolysis reactions of the iron precursors, the nucleation, and growth steps resulting in nanoparticles with wide particle size distribution which can cause a large range of blocking temperatures.

3.1.2. Thermal decomposition technique

Thermal decomposition method is a recent approach to synthesize magnetic IONs. In the presence of organic solvents, organo-metallic iron precursors are used at high temperatures to carry out this method. This method is simpler and more economical and can yield high quality and well crystallized γ-Fe_2O_3 nanoparticles with average sizes within the range of 3–17 nm. This alternative method is considered to be very efficient in the formation of high quality IONs with manageable size (Perez De Berti et al., 2013).

Thermal decomposition or thermolysis is characterized by the method in which the chemicals are treated with heat and the thermal decomposition temperature is defined by the temperature at which the substances get decomposed. This is an endothermic reaction because it uses heat to break the chemical bonds (Gonzales-Weimuller et al., 2009). When heated, precursor molecules like organometallic precursors can be converted into iron oxide nanoparticles where they decompose to iron oxide molecules. Additionally, this method depends on the organic

precursors pyrolysis of iron, e.g., Fe(CO)5 and Fe(acac)3 (Mascolo et al., 2013). Several researchers have demonstrated this method using different iron precursors.

For example, in the presence of oleic acid, monodispersed ɣ-Fe_2O_3 NPs was synthesized within the 4–16 nm size range by the decomposition of iron pentacarbonyl, Fe(CO)5, along with octyl ether by thermal decomposition at 100 °C and the formed iron-oleic acid metal complex was oxidized to produce maghemite (ɣ-Fe_2O_3) particles. Here, oleic acid acts as a capping agent. Moreover, superlattice formation can be observed because of the narrowness of the NP distribution (Hyeon et al., 2001). However, the application of magnetite for medical applications is limited as Fe(CO)5 is highly expensive, sensitive to air, and very toxic (Mascolo et al., 2013). On the other hand, in the presence of octylamine and trioctylamine, some scientists have prepared monodispersed maghemite by iron cupferronates (Cup: C6H5N(NO)O −) decomposition (Rockenberger et al., 1999). Furthermore, some have prepared Fe3O4 by heating Fe(acac)3 with oleic acid, oleylamine, and 1,2-hexadecanediol where Fe(acac)3 is more cost effective and shows low sensitivity to air compared to other acetylacetonates or acetate precursors (Sun et al., 2004). However, just like Fe(CO)5, Fe(acac)3 is also toxic, thus has limited use (Mascolo et al., 2013). Similarly, other precursors are used to synthesize IONs:

Table 1: Some precursors used in synthesizing IONs

Precursor	**Vehicle/ Catalyst**	**Temperature**	**Product**
Iron chloride (Z. Xu et al., 2010)	Sodium oleate surfactant	At 317 °C	IO nanocrystals

Iron (III) acetylacetonate $Fe(acac)_3$ (in phenyl ether) (Sun & Zeng, 2002)	Oleic acid, oleylamine, and alcohol	At 265 °C	Monodisperse magnetite nanoparticles
Iron pentacarbonyl $Fe(CO)_5$ (Woo et al., 2004)	Sodium oleate	High temperature	IO nanoparticles
Iron carboxylate salts (Yu et al., 2004)	Sodium oleate	At 320 °C	Monodisperse IO nanocrystals
Iron (III) oleate (Hufschmid et al., 2015).	Argon (Ar)	At 320 °C	IO nanoparticles
$Fe(CO)_5$ salt (Park et al., 2005)	Sodium oleate	At 320 °C	Monodisperse magnetic IO nanoparticles

Although thermal decomposition technique requires complex procedures, it synthesizes high quality monodispersed particles due to separate growth and nucleation processes. However, it

is associated with problem like the obtained nanoparticles are hydrophobic, so they can not be used directly for bio-applications. To solve this complication, it is necessary to turn them into water soluble particles where strenuous ligand exchange post-synthesis processes are performed that can lead to aggregation and loss of magnetic properties. Moreover, monodisperse nanocrystals are synthesized only in small quantities. Also, a lot of the reagents used are quite costly.

3.2. Properties of iron oxide nanoparticles

IONs are highly reactive with oxidizing agents, especially in contact with air (Huber, 2005). Every NP is covered with a fine layer of coating that has very little to no effect on the magnetic property of NPs to avoid oxidation. For this, different coating materials are used, i.e., gold, silica etc. though they affect the magnetic properties of iron particles (Wu et al., 2008). However, magnesium coating has little effect on magnetic properties but the material produced is quite complicated. For instance, iron nanoparticles are immersed in the submicrometer magnesium particles (Mahmoudi et al., 2009). To produce magnetic iron particles free from oxidation, the iron carbide coating is the most suitable method but it results in large size particles (20-100 nm), so they are not standard (Ittrich et al., 2013). Cobalt NPs are stable in air and synthesized by decomposing cobalt carbonyl in the presence of aluminum alkyls. Iron carbonyls are prepared in the similar process which have shown effective results (Huber, 2005). The significant value of IONs is attributed to their magnetic properties and well-known biological applications.

Nowadays, the exploration of iron and IONs in biological and geological sciences has led to great progress due to their many physical and chemical properties. They display various important applications which include water purification, magnetic fluid, MRI, magnetic

hyperthermia, magnetic micro-device, and drug delivery (Estelrich et al., 2015). Essential size-dependent characteristics (structural and optical) of colloidal iron and iron oxide NPs are compatible with quantum size effects and electrical structure of them. Moreover, the related synthesis methods influence their size and structure of crystal too (Dadashi et al., 2015).

3.3. Surface coatings of iron oxide nanoparticles

Iron oxides with unprotected surfaces have the inclination towards agglomeration because of the powerful magnetic attraction among particles, high energy surface, and van der Waals forces (Xia et al., 2012). As a result, the reticuloendothelial system removes the IONs agglomeration. Local Fe ions with high concentration are toxic to organisms as well due to iron dissolution. These can be inhibited by coating a layer on the ION surface making them hydrophilic which is compatible with bio-environments (Hui et al., 2011). The proper surface coating enables an effective target delivery in a related area with particle localization and is regarded as biocompatible and nontoxic. However, very few studies have been carried out to increase the magnetic particles quality. The characteristic of surface coating and geometric arrangement influence the colloid size and has an important role in biodistribution and biokinetics of nanoparticles in the body (Petcharoen & Sirivat, 2012). The type of coating mainly relies on the application, and is aimed at inflammation response or antitumor agents. Magnetic NPs can bind to proteins, antibodies, enzymes, nucleotides, or drugs. Moreover, using magnetic fields, they have the potential to be adsorbed at a specific site. Furthermore, in alternating magnetic fields, they can be heated for use in hyperthermia (Gupta & Gupta, 2005). The most effective method of synthesizing the IONs coated with biological molecules, e.g., lactobionic acid, gluconic acid, or polyacrylic acid, is coprecipitation as compared to other methods like polyol or organic solvent heating method (Dozier et al., 2010). These types of NPs are highly water soluble, have narrow size distribution, play significant roles in a lot of

biomedical applications, e.g., tissue engineering due to the biological coatings like liposome coating. Also, these NPs display hydrodynamic size in solution because of hydrogen bond formation (Mahdavi et al., 2013).

In the absence of any surface coating material, magnetic iron oxide particles have hydrophobic surfaces containing a large surface-area-to-volume ratio. Because of hydrophobic interactions between the particles, they agglomerate and form large clusters which then lead to increased particle size. These agglomerations can express strong magnetic dipole–dipole attractions between them and exhibit ferromagnetic characteristics (Hamley, 2003). When one large-particle cluster reaches another cluster, every one of them comes into the magnetic field of the neighbor. Not only the attractive forces between the particles arise, but also each particle in the magnetic field of the neighbor gets magnetized further. The adherence of the rest of the magnetic particles results in mutual magnetization which leads to the increased aggregation behavior (Gupta & Gupta, 2005). Most of the time, surface modification is crucial as the nanoparticles are magnetically attracted alongside the usual flocculation because of van der Waals forces. To stabilize the IONs, high-density coating is preferable. Usually, a polymer or a surfactant is added during preparation to avoid the aggregation of the nanoscale particulate stabilizer. Mostly, the polymers attach to the surfaces in a substrate-specific way (Ghosh et al., 2011).

3.4. Factors enhancing the efficiency of iron oxide nanoparticles

The most simple, efficient, and economical method to produce magnetic IONs, e.g., the precipitation technique. As cost-effective preparation of ION depends on the end product and its use, comparatively high cost of production is acceptable. For instance, for high end applications like in the case of drug delivery systems. At the same time, it is important to utilize

low-priced chemicals while synthesizing a product that might be used in case of less-sensitive work, e.g., waste water mitigation from toxic ions (Mohapatra & Anand, 2011).

Size of NPs should be considered as particles with smaller sizes provide a high surface-area-to-volume ratio that allows the reaction with different kinds of chemicals (aqueous and gaseous both). Moreover, the substances which are at nanoscale range are stronger for metal ions bindings (Hiemstra et al., 2004). Moreover, controlled shape, growth, nucleation, durability, dispersibility, scalability, and reproducibility are important especially for the formation of the complex magnetic nanostructures (F. Hasany et al., 2013). For example, by changing the particle shape, iron oxide can be activated and then can expose its most active catalytic site which can lead to the production of potent and cost-effective catalysts for a lot of reactions (Guo & Sun, 2012).

To ensure an effective magnetic enhancement, maintaining high magnetic susceptibility is significant. Furthermore, the width of coated IONs with metallic or non-metallic is susceptible to tailoring, and the required width can be obtained by controlling the repeat and reduction times (Mohapatra & Anand, 2011).

Particles must be nanosized (6–15 nm) and particles smaller than 15 nm consist of a single magnetic field which means a particle in a state of uniform magnetization has high saturation magnetization capability. Additionally, these particles are excreted rapidly via renal clearance and eructation (Mahmoudi et al., 2010). Furthermore, adjusted surface chemistry is significant for particular biomedical applications (Gupta et al., 2007).

For efficient MRI and optimal cell labeling, characteristically appropriate IONs should be developed. It is necessary to construct standard methods to compare different types of NPs on the basis of their cytotoxic effects and uptake efficiency. Before determining the clinical significance in cell transplantation study, the effects of IONs must be properly assessed on

cultured cells (Soenen & De Cuyper, 2009). Lastly, high co-activity and low Curie temperature should be maintained to enhance the efficiency of IONs (Huber, 2005).

Chapter 04

Types of Cancer Treatment

Biomarker Testing for Cancer Treatment

Biomarker testing is a method that looks for proteins, genes, and other substances called biomarkers or tumor markers that can provide information about tumor. Biomarkers are the substances that make tumor cells different from healthy cells. They can be determined in the tissue, blood, or bodily fluid. These biomarkers are mutations characterized by the changes in proteins, gene, or genes. They are often addressed by a 3 or 4 letter abbreviation. For example, EGFR in lung cancer which occurs due to specific genetic changes in the EGFR gene and can be treated with EGFR inhibitors that target those certain changes. Biomarkers indicate the subtype of the cancer someone has and help to determine the best treatment option for them. Some cancer drugs are effective for people carrying certain cancer subtypes (NCI, 2021).

Chemotherapy

Chemotherapy refers to the cancer treatment that uses drugs to kill tumor cells. Despite having many different types of chemotherapy drugs available, all of their mechanisms of action are the same. They prevent cancer cells from reproducing which stops their growth and spreading rate in the body. It can be used to remove cancer completely or can improve the effectiveness of other treatment options in case of combination therapy.

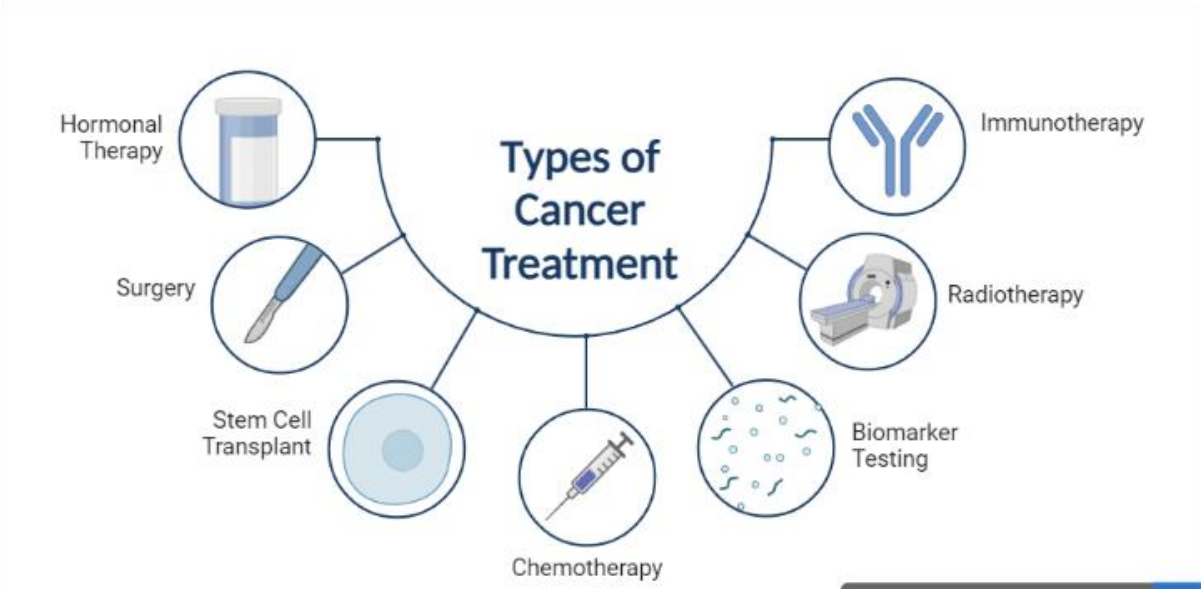

Figure 2: Different types of cancer treatment

Hormone Therapy

Hormone therapy is a treatment method that slows down or inhibits the growth of breast and prostate cancers that depend on hormones for growth. In this therapy, the drugs circulate throughout the body to find the targeted hormone, thus it is called systemic treatment. This therapy is used to shrink tumor cells before radiation therapy or surgery, thus known as neoadjuvant therapy, decreasing the chances of return and spread of cancer after initial treatment known as adjuvant therapy (NCI, 2022).

Immunotherapy

Immunotherapy is the cancer treatment that helps certain parts of the immune system to attack tumor cells. The main principle of this therapy is to stimulate a patient's immune system to fight cancer (NCI, 2019).

Radiation Therapy

Radiation therapy refers to the cancer treatment that uses high frequency of radiation to kill or shrink tumor cells. This method can be used to turn a tumor smaller in size right before surgery or to prevent any growth of the remaining tumor cells after surgery (NHS, 2020).

Stem Cell Transplant

Stem cell transplant is a process that restores stem cells that convert into blood cells in patients whose cells are damaged by high doses of radiation therapy or chemotherapy. Stem cells are undifferentiated or partially differentiated cells present in the bone marrow and possess the potential to convert into any other type of body cell. This procedure is known to be safe and effective in cancer therapy. The application of stem cells in the regeneration of other damaged cells is being investigated, so their useability is still in the experimental clinical trial. Currently, mesenchymal stem cells are being used in trials which are being taken from the bone marrow, connective tissues, and fat tissues (Naji et al., 2019).

Surgery

When used in treating cancer, surgery is a process where a surgeon removes the entire tumor from the body.

Targeted Therapy

Targeted therapy is defined as the cancer treatment that uses drugs or other substances designed to target the changes in cancer cells which help them in growing, dividing, and spreading. Sometimes, these drugs or other substances are interchangeably used as molecularly targeted therapies, molecularly targeted drugs, and precision medicines. The mechanism of action of

them is to interfere with growth molecules that results in blocking the growth and spreading of cancer (Shuel, 2022). On the basis of their mechanism or target site, the targeted cell agents can be classified. Some of the enzymes work as indicators for growth of tumor cells and some targeted therapies can block these enzymes which are known as enzyme inhibitors. Inhibition of these cell signals can stop the growth and spread of cancerous cells (Citri & Yarden, 2006).

4.1. Magnetic hyperthermia to treat cancer

Magnetic hyperthermia therapy (MHT) was first introduced in 1957 to treat cancers by selectively heating the tumors that had metastasised to the lymph nodes, (Mahmoudi et al., 2018). The magnetic nanoparticles (MNPs) have the capability to produce heat when exposed to an alternating magnetic field (AMF) and MHT uses this heat to kill cancer cells. Because of their numerous benefits towards effective anticancer treatment, e.g., deep tissue invasion, high biosafety, and selective tumor killing without affecting healthy tissus, it has evolved into a one of most well-researched topics in the nanomedical field. Because of all the therapeutic benefits, they are incorporated in the glioblastoma and prostate cancer therapy. Further, several clinical trials are observed for investigating pancreatic cancer treatment (Espinosa et al., 2018). It aids in understanding intracellular hyperthermia, since it carries therapeutic heating directly to the targeted cells, and through the cell-targeting ligands (antibody/ peptide) conjugation with MNPs without reducing its efficiency, it can be further improved (Ho et al., 2011). For example, the targeting of solid tumors can be enhanced by conjugation of folate receptors (Nanjing, 2011).

However, there are still many challenges that have to be beaten for MHT to advance and to utilize its utmost significance as a suitable choice for cancer therapy. Therefore, the efficacy of MHT should be enhanced. Primarily, the method of MH focuses on heating using the MNPs for therapeutic purposes. It involves the rise of local temperature of tumor cells within the range

of 43-46 ºC leading to the change in physiology of the tumor cell which then eventually results in their apoptosis or necrosis (Hildebrandt et al., 2002). The primary strategy to enhance the therapeutic efficiency is to improve the thermal conversion efficacy of MNPs as it is important that an adequate amount of heat needs to be delivered within the entire tumor mass without affecting the surrounding healthy cells. IONs are broadly explored as MH agents among various MNPs because of their biodegradability and high biocompatibility. However, their thermal conversion efficiency is not sufficient, hence their decreased magnetic susceptibility has been presented as a major challenge in case of practical applications. To overcome this, further research has been done to enhance the magnetic susceptibility to accomplish improved induction heating properties by introducing strategies like particle size modulation (Ma et al., 2004), composition control, shape manipulation, and surface modification (Sugumaran et al., 2019).

Chapter 05

Cancer Treatment with Magnetic Iron Oxide Nanoparticles

5.1. As contrast agents for Magnetic Resonance Imaging

MRI is a method of non-invasive imaging which is usually utilized as a clinical device for the treatment of different types of cancer. It is favorable because it gives better spatial resolution, has great penetration ability, does not emit any harmful ionizing radiation compared to other clinical imaging tools (Kim et al., 2017). Contrast agents such as gadolinium-based complexes are used commonly to enhance image contrast.

Gadolinium-based chelates are considered as the primary T_1 contrast agents for MRI but their toxicity causes harmful effects and the FDA has warned about their possible retention in the human body. Other side effects include fatal nephrogenic systemic fibrosis, brain lesions etc. and the reasons being short blood half-life of Gd^{3+}-based contrast agents (GBCAs) and accumulation of Gd in the brain in long-term use. As an improved alternative, MNPs have promising potential due to their non-toxic and biodegradable behavior (Taheri et al., 2016). However, MNPs are inherently MR contrast agents that are particularly suited to be theranostic agents as they act as both therapeutic and diagnostic due to their multifunctional potential when combined with magnetic fields. This occurs due to their efficient contrast mechanisms, i.e., both negative and positive which can be exploited (Girard et al., 2012).

Magnetic IONs have continued to gain significant attention for their application in countless biomedical technology (Sun et al., 2008). The center of this interest arises from the distinctive combination of innate biocompatibility with reaction to magnetic fields that results in various uses (Bárcena et al., 2009). If formulated appropriately, the magnetic properties of IONs can be altered for application along with static magnetic fields to impart contrast for MRI. These

particles which have suitable magnetic anisotropy can produce heat when introduced to an alternating magnetic field (AMF) and the amount of heat produced can be modified by controlling the magneto-structural properties of IONs. Magnetic ION-mediated heat therapy, also known as hyperthermia, is of singular interest for image-guided and targeted therapy of cancer (Dennis & Ivkov, 2013).

Compared to GBCAs, iron oxide NPs significantly shorten transverse relaxation times. They have shown flexible surface chemistry, long blood half-lives, and low toxicity (Chiarelli et al., 2017). Moreover, they are easily removed from the body, and naturally degrades in which they are metabolized into the hemoglobin of the body (Briley-Saebo et al., 2004). A lot of components of IONs have been approved as T_2 contrast agents already by the FDA (Fang et al., 2009).

Although the treatment of cancer by MRI has gained significant progress, their ability to differentiate cancer cells from healthy cells has yet to be achieved (Koikkalainen et al., 2016). The MRI resolution can be enhanced using contrast agents which sharpens the contrast by shortening either the longitudinal (T_1) or transverse (T_2) relaxation times of water protons. T_1 contrast agents enhance the T_1 signal in T_1-weighted imaging that leads to a positive or brighter contrast enhancement. On the contrary, T_2 contrast agents decrease the T_2 signal in T_2-weighted imaging that leads to a negative or dark contrast enhancement (Peng et al., 2016). The primary physicochemical properties of IONs such as core size, shape, chemistry of surface coating, chemical doping, and composition control the T_1 contrast enhancement. These nanoparticles differ in size and surface coating which greatly affect their uptake, biodistribution, and blood half-life. In addition, external variables like applied magnetic field have an effect on the enhancement of contrast as well by controlling the Larmor frequency. Furthermore, agglomeration of particles can improve the contrast enhancement radically by regulating the agent relaxivities and it can be applied to develop a T_1-T_2 switchable contrast agent.

There are many commercially available drugs that contain superparamagnetic IONs, e.g., Resovist (Schering, EU, Japan), Endorem (Guerbet, EU), and Feridex (Berlex, USA). They are commonly used for spleen and liver cancer treatment. Some of these medium sized particles are coated with dextran (Feridex, Endorem) and some are treated with alkali with low molecular weight carboxydextran (Resovist) (Lawaczeck et al., 2004).

5.2. Cell tracking with iron oxide nanoparticles:

In 1993, MRI cell tracking was developed to observe survival of cell and migration after tumor grafting. The time course of the first migration of cell in vivo was addressed back in 2001. The significant strength of iron oxide enables researchers to achieve success in tracking single cells in vivo which includes stem cells, neural cells, and dendritic cells (DCs) (Korchinski et al., 2015). Various iron oxide contrast agents along with MRI are used to improve tissue contrast for cell tracking. IONs are widely applied as a negative contrast agent which causes hypointense contrast (Stoll & Bendszus, 2010). ION-based contrast is normally more potent than the most common contrast agent, gadolinium (Gd).

A general study framework for cancer treatment requires the injection of a cancerous cell line into an animal host. A lot of researchers have labeled cancer cells without expecting to imaging the immune response but to only observe the growth and spread of cancer cell in reaction to the therapy. With current progress in imaging of single cell, many researchers have been successful to detect single cancer cells in liver cancer but this still has not been tested in a living animal model. Several studies to visualize tumors using IONs have been conducted (Townson et al., 2009).

There are several key applications of IONs in glioblastoma multiforme (GBM) or simply glioblastoma which is a rapidly growing aggressive type of CNS tumor with poor prognosis that occurs in the spinal cord or brain. It is generated from astrocytes which are the cells that

support nerve cells. Firstly, multifunctional IONs are used to ease the delivery of cytotoxic drugs to GBM. The IONs coatings can be altered to adhere to the receptors present in the tumor surface. For instance, epidermal growth factor receptors are overexpressed in most GBM tumors. Now, the altered IONs can adhere to cytotoxic drugs which permits more potent delivery to cancer cells. Evidence has been found that therapy with an altered IONs attached with a cytotoxic drug (e.g., cetuximab) leads to great anticancer effect as oppose to non-attached cetuximab and shows enhanced efficiency of cancer drug delivery to targeted cells (Kaluzova et al., 2015). Using modified IONs, similar studies have been performed to use anticancer peptides (chlorotoxin) (Shevtsov et al., 2015).

IONs are incorporated as blood-pool agents as well to separate true progression from pseudoprogression of tumors. Pseudoprogression appears to be very similar to the recurrence of cancer on Gd-enhanced T1-weighted images due to radiation necrosis. The recent process to identify pseudoprogression is not reliable because it has negative correlation with survival chances (Nasseri et al., 2014). However, using dynamic contrast-enhanced MRI, pseudoprogression can be identified to measure cerebral blood volume (CBV). If the CBV is high, it indicates the presence of a tumor whereas deviation from normal or low level of CBV suggests pseudoprogression (Gahramanov et al., 2013).

While Gd is most commonly used as a contrast agent to determine CBV, in case of GBM, the Blood brain barrier (BBB) is usually compromised leading to leaking of contrast agents into the tumor cell. This hinders the accurate CBV calculation and a leaking factor is often required to calculate the true CBV (Gahramanov et al., 2013). In contrast, ION, like ferumoxytol, works as a blood-pool agent and does not present any leakage of contrast even when the BBB is penetrated. Ferumoxytol exhibits reliable evidence to distinguish pseudoprogression from recurrence of cancer. When calculated using ferumoxytol, the abnormal regions with a low CBV indicate pseudoprogression which is related to the significantly prolonged survival and

abnormal regions with high CBV suggest true progression. Therefore, a leaking correction factor is not required to calculate CBV for ferumoxytol compared to Gd. Hence, Ferumoxytol is considered as a potential blood-pool agent in certain situations like where the BBB is a concern (Varallyay et al., 2009).

Immunotherapy is another option of treating cancer where the immune system is suppressed in cases including GBM (Yang et al., 2010). IONs are promising particles to label immune cells and evaluate the effectiveness of this kind of treatment method. Studies show that amphotericin B (AmpB) can suppress GBM, activate innate immunity, and prolong the lifespan of mice. AmpB amplifies the total count of circulating monocytes and proinflammatory macrophages in the tumor. And when these monocytes are labeled with IONs, which means upregulating and infiltrating blood monocytes into the tumor, drug response of AmpB can be determined way before there is any indication of tumor volume change (Sarkar et al., 2014).

Lastly, to determine the efficacy of cancer immunotherapy, IONs are used in DC-based vaccines as well. The DC vaccine therapy focuses on the migration of vaccinated DCs to lymph nodes where it activates T cells and induces an anticancer response. Here, IONs are labeled with vaccinated DCs in vivo to track their location to observe treatment response. IONs leave DC viability greatly unimpaired (Dekaban et al., 2013). When magnetically labeled DCs are administered at the sites of inflammation, a dose-dependent signal drop is detected in the lymph node confirming the presence of immune cells along with iron in the lymph nodes (Baumjohann et al., 2006).

5.3. As drug carriers for targeted specific drug delivery

To improve the anticancer efficacy while controlling toxicity to healthy tissues, the selective delivery of therapeutic substances directly in the tumor mass is significant (Chang et al. 2007). It is often challenging to deliver drugs containing small molecules to the tumor cell because of

their drug solubility, fast secretion, and low intra-tumor accumulation. To minimize this limitation, nanoparticle delivery vehicles can reconstruct the tissue distribution profile and pharmacokinetics in favor of tumor specific accumulation. Through enhanced permeability and retention effect, nanoparticle-based drugs can accumulate in high concentrations in some solid tumors compared to free drugs. Moreover, via receptor-mediated internalization, nanoparticles that actively target tumor can alter the intracellular biodistribution and elevate the local concentration of drug within the tumor cells. The imaging power of magnetic iron oxide NPs permits quantification and monitoring of the iron oxide NPs-drug complex with the assistance of MRI in vivo.

Therapeutic entities are built in the IONs by loading them on the surface or entrapping them within the particles themselves. These entities include peptides, proteins, nucleic acids, small molecular drugs etc. Usually, the loaded drugs are delivered to the target site and released by dissolution, diffusion, rupture of vehicle, pH-sensitive dissociation, or endocytosis of the conjugations. These delivery carriers possess many conveniences including water-solubility, little to no toxicity, are biodegradable, biocompatibility, have long blood retention time, ability of further modification and more. Lastly, monitoring of therapeutic response and estimation of tissue drug levels at the same time is also possible by this therapeutic iron oxide conjugations (Winter et al. 2004).

To achieve effective delivery, some of the traditional anti-tumor agents, methotrexate (MTX), cisplatin (DDP), doxorubicin (DOX) etc., are conjugated with tumor-targeted IONs. For example, folate receptor-targeted iron oxide NPs are developed to deliver DOX to cancer cells (Grailer et al. 2010).

In the treatment of cancers, one of the most commonly used chemotherapy agents is Cisplatin (DDP). It is widely used for head and neck, non-small lung cancer, ovarian, testicular, and bladder cancers. However, about one of three patients who goes under DDP treatment, suffers

from irreversible kidney damage, also known as cumulative nephrotoxicity, which is the dose limiting toxicity of this drug. To reduce this toxicity, it is necessary to develop a targeted delivery system of DDP to cancer cells only enhancing its therapeutic index. Here, IONs can be used as carriers of DDP for specific therapeutic applications. Using the nanoprecipitation method, DDP porous is loaded into pegylated hollow nanoparticles (PHNPs) of iron oxide (Fe_3O_4). Studies show that about 25% loading efficacy can be achieved in this way. On the Pt-PHNP surface, Herceptin is attached to the amine-reactive groups by covalent bond which does not affect the Herceptin activity. Outcomes indicate that after internalization by cells, the Her-Pt-PHNPs can release the DDP in the acidic lysosomes or endosomes and can result in increased cytotoxicity of DDP (Peng et al. 2009).

Methotrexate (MTX) works as a therapeutic agent for tumor cells that overexpress folate receptor (FR) on the cell surface. It also works as a targeting molecule for FR. The carboxyl end groups of this agent help to conjugate the IONs with amine groups. MTX-IONs uptake by FR-overexpressing tumor cells is very high compared to that of FR-negative control cells. About 418 MTX molecules with a core size of 10nm can be loaded into each IONs. Therefore, this approach exhibits high drug loading potency. At low pH, this loaded MTX then is freed within the lysosomes only right after internalization by the targeted cells. Moreover, this process can be observed by MRI in real-time in vivo (Sun et al. 2005).

Chapter 06

Conclusion and Future Perspectives

Extensive research and the fabrication of magnetic IONs during the last decade have given rise to a better comprehension of the potential biological and biomedical significance of iron oxide nanoparticles. A broad range of modern IONs have been developed for cancer targeted drug delivery and imaging. However, there are many aspects that are yet to be explored and quite challenging to overcome. For example- specific agglomeration in the cancer cells and very little uptake in healthy organs or tissue by adopting suitable tumor-targeted ligands. Modification of surface, suitable size and charge of nanoparticles for efficient delivery are hard to achieve as well. Other challenges include maintaining the stability of IO nanotherapeutic agents, regulating the blood circulation time, and designing the smart cancer-targeted IONs in a way so that loaded drugs are released only within the targeted cancer cells.

In recent years, the possibility of manipulating the size and shape of particles along with the function of the surface has provided a significant amount of interest in the field of research and development. Magnetic IONs benefit from being applied in many sectors like hyperthermia and being delivered to a specific site within the body via using an alternating magnetic field. Their large surface area to volume ratio allows them a high level of substitution which enables them to be appropriate for drug delivery.

Recently, there is increasing concern regarding the safety of IO nanotherapeutic delivery systems. Despite the fact that vast examination has been performed in laboratory animals for drug delivery and magnetic hyperthermia using IONs, interpreting this into acceptable treatment options for human beings presents a huge obstacle. To assure patient safety, it is important to evaluate the impacts of their size, shape, dosage, and substitution before application. If any kind of adverse effects or toxicity issues are detected, they should be

addressed, reported, and solved. Although primary administration of IONs in hyperthermia and drug delivery systems have proved to be effective in the lab, stability tests, expansive in vivo and in vitro studies are required before clinical use.

Although several animal studies do not indicate any serious noticeable toxicities, most of the accessible information is obtained from experiments conducted on mice solely followed by very few studies done in rats, monkeys, and dogs. Moreover, the subchronic and chronic toxicity tests for most IONs have not been carried out yet. The effects of use of IONs for an extended period of time and their in vivo pharmacokinetic and pharmacodynamic alterations are not well established (Peng et al., 2008). As most of the nanotherapeutic delivery strategies are non-targeted, in-depth research is needed to apply tumor-targeted nanoparticles safely as drug delivery carriers. Some other course of actions can be implemented in order to overcome limitations. Firstly, in diverse fields, critical and systematic study is essential to design and formulate IONs for diverse applications. Secondly, with the implementation of multidisciplinary approaches, it is warranted to contemplate the formation of regulatory organizations to establish the safe and effective use of nanotechnology. And thirdly, a specific, simple mechanism and strong connection must be developed between researchers and institutions to establish ideal standards and common platforms for preclinical trials and in vivo clinical studies.

References

Ali, A., Zafar, H., Zia, M., ul Haq, I., Phull, A. R., Ali, J. S., & Hussain, A. (2016). Synthesis, characterization, applications, and challenges of iron oxide nanoparticles. *Nanotechnology, Science and Applications*, *9*, 49–67. https://doi.org/10.2147/NSA.S99986

Arruebo, M., Vilaboa, N., Sáez-Gutierrez, B., Lambea, J., Tres, A., Valladares, M., & González-Fernández, Á. (2011). Assessment of the evolution of cancer treatment therapies. *Cancers*, *3*(3), 3279–3330. https://doi.org/10.3390/cancers3033279

Bandhu, A., Mukherjee, S., Acharya, S., Modak, S., Brahma, S. K., Das, D., & Chakrabarti, P. K. (2009). Dynamic magnetic behaviour and Mössbauer effect measurements of magnetite nanoparticles prepared by a new technique in the co-precipitation method. *Solid State Communications*, *149*(41–42), 1790–1794. https://doi.org/10.1016/j.ssc.2009.07.018

Banerjee, S. S., & Chen, D. H. (2007). Glucose-grafted gum arabic modified magnetic nanoparticles: Preparation and specific interaction with Concanavalin A. *Chemistry of Materials*, *19*(15), 3667–3672. https://doi.org/10.1021/cm070461k

Bárcena, C., Sra, A. K., & Gao, J. (2009). Applications of magnetic nanoparticles in biomedicine. *Nanoscale Magnetic Materials and Applications*, 591–626. https://doi.org/10.1007/978-0-387-85600-1_20

Baumjohann, D., Hess, A., Budinsky, L., Brune, K., Schuler, G., & Lutz, M. B. (2006). In vivo magnetic resonance imaging of dendritic cell migration into the draining lymph nodes of mice. *European Journal of Immunology*, *36*(9), 2544–2555. https://doi.org/10.1002/eji.200535742

Beal, E. G. (2017). Document 4. In *The Origin of Likin, 1835–1864* (pp. 101–102). https://doi.org/10.2307/j.ctt1tg5hw3.13

Binandeh, M. (2022). Performance of unique magnetic nanoparticles in biomedicine. *European Journal of Medicinal Chemistry Reports*, *6*, 100072. https://doi.org/10.1016/j.ejmcr.2022.100072

Blanco-Andujar C, Teran FJ, Ortega D. Mahmoudi M, Laurent S, E. (2018). Iron Oxide Nanoparticles for Biomedical Applications. *Iron Oxide Nanoparticles for Biomedical Applications*. https://doi.org/10.1016/c2015-0-06003-8

Briley-Saebo, K., Bjørnerud, A., Grant, D., Ahlstrom, H., Berg, T., & Kindberg, G. M. (2004). Hepatic cellular distribution and degradation of iron oxide nanoparticles following single intravenous injection in rats: Implications for magnetic resonance imaging. *Cell and Tissue Research*, *316*(3), 315–323. https://doi.org/10.1007/s00441-004-0884-8

Charmsaz, S., Collins, D. M., Perry, A. S., & Prencipe, M. (2019). Novel strategies for cancer treatment: Highlights from the 55th IACR annual conference. *Cancers*, *11*(8). https://doi.org/10.3390/cancers11081125

Chiarelli, P. A., Revia, R. A., Stephen, Z. R., Wang, K., Jeon, M., Nelson, V., Kievit, F. M., Sham, J., Ellenbogen, R. G., Kiem, H. P., & Zhang, M. (2017). Nanoparticle Biokinetics in Mice and Nonhuman Primates. *ACS Nano*, *11*(9), 9514–9524. https://doi.org/10.1021/acsnano.7b05377

Citri, A., & Yarden, Y. (2006). EGF-ERBB signalling: Towards the systems level. *Nature Reviews Molecular Cell Biology*, *7*(7), 505–516. https://doi.org/10.1038/nrm1962

Clerc, P., Jeanjean, P., Hallalli, N., Gougeon, M., Pipy, B., Carrey, J., Fourmy, D., & Gigoux, V. (2018). Targeted Magnetic Intra-Lysosomal Hyperthermia produces lysosomal

reactive oxygen species and causes Caspase-1 dependent cell death. *Journal of Controlled Release*, *270*, 120–134. https://doi.org/10.1016/j.jconrel.2017.11.050

Corot, C., Robert, P., Idée, J. M., & Port, M. (2006). Recent advances in iron oxide nanocrystal technology for medical imaging. *Advanced Drug Delivery Reviews*, *58*(14), 1471–1504. https://doi.org/10.1016/j.addr.2006.09.013

Cuzick, J., Sestak, I., Pinder, S. E., Ellis, I. O., Forsyth, S., & Nigel, J. (2010). *The Lancet Oncology*. *12*(1), 21–29.

Dadashi, S., Poursalehi, R., & Delavari, H. (2015). Structural and Optical Properties of Pure Iron and Iron Oxide Nanoparticles Prepared via Pulsed Nd:YAG Laser Ablation in Liquid. *Procedia Materials Science*, *11*, 722–726. https://doi.org/10.1016/j.mspro.2015.11.052

Daou, T. J., Pourroy, G., Bégin-Colin, S., Grenèche, J. M., Ulhaq-Bouillet, C., Legaré, P., Bernhardt, P., Leuvrey, C., & Rogez, G. (2006). Hydrothermal synthesis of monodisperse magnetite nanoparticles. *Chemistry of Materials*, *18*(18), 4399–4404. https://doi.org/10.1021/cm060805r

Debela, D. T., Muzazu, S. G., Heraro, K. D., Ndalama, M. T., Mesele, B. W., Haile, D. C., Kitui, S. K., & Manyazewal, T. (2021). New approaches and procedures for cancer treatment: Current perspectives. *SAGE Open Medicine*, *9*, 205031212110343. https://doi.org/10.1177/20503121211034366

Dekaban, G. A., Hamilton, A. M., Fink, C. A., Au, B., de Chickera, S. N., Ribot, E. J., & Foster, P. J. (2013). Tracking and evaluation of dendritic cell migration by cellular magnetic resonance imaging. *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology*, *5*(5), 469–483. https://doi.org/10.1002/wnan.1227

Dennis, C. L., & Ivkov, R. (2013). Physics of heat generation using magnetic nanoparticles for

hyperthermia. *International Journal of Hyperthermia*, *29*(8), 715–729. https://doi.org/10.3109/02656736.2013.836758

Dozier, D., Palchoudhury, S., & Bao, Y. (2010). Synthesis of iron oxide nanoparticles with biological coatings. *The Journal of Science and Health at the …*, 16–18. http://scholar.google.com/scholar?hl=en&btnG=Search&q=intitle:Synthesis+of+Iron+Oxide+Nanoparticles+with+Biological+Coatings#0

El-Readi, M. Z., & Althubiti, M. A. (2019). Cancer Nanomedicine: A New Era of Successful Targeted Therapy. *Journal of Nanomaterials*, *2019*. https://doi.org/10.1155/2019/4927312

Espinosa, A., Kolosnjaj-Tabi, J., Abou-Hassan, A., Plan Sangnier, A., Curcio, A., Silva, A. K. A., Di Corato, R., Neveu, S., Pellegrino, T., Liz-Marzán, L. M., & Wilhelm, C. (2018). Magnetic (Hyper)Thermia or Photothermia? Progressive Comparison of Iron Oxide and Gold Nanoparticles Heating in Water, in Cells, and In Vivo. *Advanced Functional Materials*, *28*(37). https://doi.org/10.1002/adfm.201803660

Estelrich, J., Escribano, E., Queralt, J., & Busquets, M. A. (2015). Iron oxide nanoparticles for magnetically-guided and magnetically-responsive drug delivery. *International Journal of Molecular Sciences*, *16*(4), 8070–8101. https://doi.org/10.3390/ijms16048070

F. Hasany, S., Ahmed, I., J, R., & Rehman, A. (2013). Systematic Review of the Preparation Techniques of Iron Oxide Magnetic Nanoparticles. *Nanoscience and Nanotechnology*, *2*(6), 148–158. https://doi.org/10.5923/j.nn.20120206.01

Fang, C., Bhattarai, N., Sun, C., & Zhang, M. (2009). Functionalized nanoparticles with long-term stability in biological media. *Small*, *5*(14), 1637–1641. https://doi.org/10.1002/smll.200801647

Fleige, G., Nolte, C., Synowitz, M., Seeberger, F., Kettenmann, H., & Zimmer, C. (2001). Magnetic labeling of activated microglia in experimental gliomas. *Neoplasia*, *3*(6), 489–499. https://doi.org/10.1038/sj.neo.7900176

Gahramanov, S., Muldoon, L. L., Varallyay, C. G., Li, X., Kraemer, D. F., Fu, R., Hamilton, B. E., Rooney, W. D., & Neuwelt, E. A. (2013). Pseudoprogression of glioblastoma after chemo- and radiation therapy: Diagnosis by using dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging with ferumoxytol versus gadoteridol and correlation with survival. *Radiology*, *266*(3), 842–852. https://doi.org/10.1148/radiol.12111472

Geng, B., Liu, X., Ma, J., & Du, Q. (2007). A new nonhydrolytic single-precursor approach to surfactant-capped nanocrystals of transition metal sulfides. *Materials Science and Engineering B: Solid-State Materials for Advanced Technology*, *145*(1–3), 17–22. https://doi.org/10.1016/j.mseb.2007.09.065

Ghosh, S., Jiang, W., McClements, J. D., & Xing, B. (2011). Colloidal stability of magnetic iron oxide nanoparticles: Influence of natural organic matter and synthetic polyelectrolytes. *Langmuir*, *27*(13), 8036–8043. https://doi.org/10.1021/la200772e

Girard, O. M., Ramirez, R., Mccarty, S., & Mattrey, R. F. (2012). Toward absolute quantification of iron oxide nanoparticles as well as cell internalized fraction using multiparametric MRI. *Contrast Media and Molecular Imaging*, *7*(4), 411–417. https://doi.org/10.1002/cmmi.1467

Gonzales-Weimuller, M., Zeisberger, M., & Krishnan, K. M. (2009). Size-dependant heating rates of iron oxide nanoparticles for magnetic fluid hyperthermia. *Journal of Magnetism and Magnetic Materials*, *321*(13), 1947–1950. https://doi.org/10.1016/j.jmmm.2008.12.017

Guo, S., & Sun, S. (2012). FePt nanoparticles assembled on graphene as enhanced catalyst for oxygen reduction reaction. *Journal of the American Chemical Society*, *134*(5), 2492–2495. https://doi.org/10.1021/ja2104334

Gupta, A. K., & Gupta, M. (2005). Synthesis and surface engineering of iron oxide nanoparticles for biomedical applications. *Biomaterials*, *26*(18), 3995–4021. https://doi.org/10.1016/j.biomaterials.2004.10.012

Gupta, A. K., Naregalkar, R. R., Vaidya, V. D., & Gupta, M. (2007). Recent advances on surface engineering of magnetic iron oxide nanoparticles and their biomedical applications. *Nanomedicine*, *2*(1), 23–39. https://doi.org/10.2217/17435889.2.1.23

Hamley, I. W. (2003). Nanotechnology with soft materials. *Angewandte Chemie - International Edition*, *42*(15), 1692–1712. https://doi.org/10.1002/anie.200200546

He, X., Wu, X., Cai, X., Lin, S., Xie, M., Zhu, X., & Yan, D. (2012). Functionalization of magnetic nanoparticles with dendritic-linear-brush- like triblock copolymers and their drug release properties. *Langmuir*, *28*(32), 11929–11938. https://doi.org/10.1021/la302546m

Hiemstra, T., Rahnemaie, R., & Van Riemsdijk, W. H. (2004). Surface complexation of carbonate on goethite: IR spectroscopy, structure and charge distribution. *Journal of Colloid and Interface Science*, *278*(2), 282–290. https://doi.org/10.1016/j.jcis.2004.06.014

Hildebrandt, B., Wust, P., Ahlers, O., Dieing, A., Sreenivasa, G., Kerner, T., Felix, R., & Riess, H. (2002). The cellular and molecular basis of hyperthermia. *Critical Reviews in Oncology/Hematology*, *43*(1), 33–56. https://doi.org/10.1016/S1040-8428(01)00179-2

Ho, D., Sun, X., & Sun, S. (2011). Monodisperse magnetic nanoparticles for theranostic

applications. *Accounts of Chemical Research*, *44*(10), 875–882. https://doi.org/10.1021/ar200090c

Hua, M. Y., Yang, H. W., Liu, H. L., Tsai, R. Y., Pang, S. T., Chuang, K. L., Chang, Y. S., Hwang, T. L., Chang, Y. H., Chuang, H. C., & Chuang, C. K. (2011). Superhigh-magnetization nanocarrier as a doxorubicin delivery platform for magnetic targeting therapy. *Biomaterials*, *32*(34), 8999–9010. https://doi.org/10.1016/j.biomaterials.2011.08.014

Huber, D. L. (2005). Synthesis, properties, and applications of iron nanoparticles. *Small*, *1*(5), 482–501. https://doi.org/10.1002/smll.200500006

Hufschmid, R., Arami, H., Ferguson, R. M., Gonzales, M., Teeman, E., Brush, L. N., Browning, N. D., & Krishnan, K. M. (2015). Synthesis of phase-pure and monodisperse iron oxide nanoparticles by thermal decomposition. *Nanoscale*, *7*(25), 11142–11154. https://doi.org/10.1039/c5nr01651g

Hui, C., Shen, C., Tian, J., Bao, L., Ding, H., Li, C., Tian, Y., Shi, X., & Gao, H. J. (2011). Core-shell Fe3O4@SiO2 nanoparticles synthesized with well-dispersed hydrophilic Fe3O4 seeds. *Nanoscale*, *3*(2), 701–705. https://doi.org/10.1039/c0nr00497a

Hyeon, T., Su Seong Lee, Park, J., Chung, Y., & Hyon Bin Na. (2001). Synthesis of highly crystalline and monodisperse maghemite nanocrystallites without a size-selection process. *Journal of the American Chemical Society*, *123*(51), 12798–12801. https://doi.org/10.1021/ja016812s

I. Sharifi, H. Shokrollahi, S. A. (2012). Journal of Magnetism and Magnetic Materials: Foreword. In *Journal of Magnetism and Magnetic Materials* (Vols. 272–276, Issue I). https://doi.org/10.1016/j.jmmm.2004.02.018

Ittrich, H., Peldschus, K., Raabe, N., Kaul, M., & Adam, G. (2013). Superparamagnetic iron oxide nanoparticles in biomedicine: Applications and developments in diagnostics and therapy. *RoFo Fortschritte Auf Dem Gebiet Der Rontgenstrahlen Und Der Bildgebenden Verfahren*, *185*(12), 1149–1166. https://doi.org/10.1055/s-0033-1335438

Jörg Rockenberger, Erik C. Scher, and A. P. A. (1999). A New Nonhydrolytic Single-Precursor Approach to Surfactant-Capped Nanocrystals of Transition Metal Oxides. *Journal of the American Chemical Society*.

Kaluzova, M., Bouras, A., Machaidze, R., & Hadjipanayis, C. G. (2015). Targeted therapy of glioblastoma stem-like cells and tumor nonstem cells using cetuximab-conjugated iron-oxide nanoparticles. *Oncotarget*, *6*(11), 8788–8806. https://doi.org/10.18632/oncotarget.3554

Kim, J., Lee, N., & Hyeon, T. (2017). Recent development of nanoparticles for molecular imaging. *Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences*, *375*(2107). https://doi.org/10.1098/rsta.2017.0022

Koikkalainen, J., Rhodius-Meester, H., Tolonen, A., Barkhof, F., Tijms, B., Lemstra, A. W., Tong, T., Guerrero, R., Schuh, A., Ledig, C., Rueckert, D., Soininen, H., Remes, A. M., Waldemar, G., Hasselbalch, S., Mecocci, P., Van Der Flier, W., & Lötjönen, J. (2016). Differential diagnosis of neurodegenerative diseases using structural MRI data. *NeuroImage: Clinical*, *11*, 435–449. https://doi.org/10.1016/j.nicl.2016.02.019

Korchinski, D. J., Taha, M., Yang, R., Nathoo, N., & Dunn, J. F. (2015). Iron Oxide as an Mri Contrast Agent for Cell Tracking: Supplementary Issue. *Magnetic Resonance Insights*, *8s1*, MRI.S23557. https://doi.org/10.4137/mri.s23557

Laurent, S., Forge, D., Port, M., Roch, A., Robic, C., Vander Elst, L., & Muller, R. N. (2008). Magnetic iron oxide nanoparticles: Synthesis, stabilization, vectorization,

physicochemical characterizations and biological applications. *Chemical Reviews*, *108*(6), 2064–2110. https://doi.org/10.1021/cr068445e

Laurent, S., Forge, D., Port, M., Roch, A., Robic, C., Vander Elst, L., & N. Muller, R. (2008). Magnetic Iron Oxide Nanoparticles: Synthesis, Stabilization, Vectorization, Physicochemical Characterizations, and Biological Applications. *Chemical Reviews*, *108*(6), 2064–2110. https://doi.org/10.1021/cr068445e

Lawaczeck, R., Menzel, M., & Pietsch, H. (2004). Superparamagnetic iron oxide particles: Contrast media for magnetic resonance imaging. *Applied Organometallic Chemistry*, *18*(10), 506–513. https://doi.org/10.1002/aoc.753

Liu, X., Zhang, Y., Wang, Y., Zhu, W., Li, G., Ma, X., Zhang, Y., Chen, S., Tiwari, S., Shi, K., Zhang, S., Fan, H. M., Zhao, Y. X., & Liang, X. J. (2020). Comprehensive understanding of magnetic hyperthermia for improving antitumor therapeutic efficacy. *Theranostics*, *10*(8), 3793–3815. https://doi.org/10.7150/thno.40805

Long, C. M., Van Laarhoven, H. W. M., Bulte, J. W. M., & Levitsky, H. I. (2009). Magnetovacci nation as a novel method to assess and quantify dendritic cell tumor antigen capture and delivery to lymph nodes. *Cancer Research*, *69*(7), 3180–3187. https://doi.org/10.1158/0008-5472.CAN-08-3691

Lu, Y., Yin, Y., Mayers, B. T., & Xia, Y. (2002). Modifying the Surface Properties of Superparamagnetic Iron Oxide Nanoparticles through a Sol-Gel Approach. *Nano Letters*, *2*(3), 183–186. https://doi.org/10.1021/nl015681q

Ma, M., Wu, Y., Zhou, J., Sun, Y., Zhang, Y., & Gu, N. (2004). Size dependence of specific power absorption of Fe3O 4 particles in AC magnetic field. *Journal of Magnetism and Magnetic Materials*, *268*(1–2), 33–39. https://doi.org/10.1016/S0304-8853(03)00426-8

Mahdavi, M., Ahmad, M. Bin, Haron, M. J., Namvar, F., Nadi, B., Ab Rahman, M. Z., & Amin, J. (2013). Synthesis, surface modification and characterisation of biocompatible magnetic iron oxide nanoparticles for biomedical applications. *Molecules*, *18*(7), 7533–7548. https://doi.org/10.3390/molecules18077533

Mahdi Karimi, a Amir Ghasemi, b Parham Sahandi Zangabad, b Reza Rahighi, cd S. Masoud Moosavi Basri, ef H. Mirshekari, g M. Amiri, b Z. Shafaei Pishabad, h A. Aslani, b M. Bozorgomid, i D. Ghosh, j A. Beyzavi, k A. Vaseghi, l A. R. Aref, m L. Haghani, n S. B. and M. R. H. (2016). Smart micro/nanoparticles in stimulus-responsive drug/gene delivery systems. *Chemical Society Reviews*.

Mahhouti, Z., El Moussaoui, H., Mahfoud, T., Hamedoun, M., El Marssi, M., Lahmar, A., El Kenz, A., & Benyoussef, A. (2019). Chemical synthesis and magnetic properties of monodisperse cobalt ferrite nanoparticles. *Journal of Materials Science: Materials in Electronics*, *30*(16), 14913–14922. https://doi.org/10.1007/s10854-019-01863-3

Mahmoudi, K., Bouras, A., Bozec, D., Ivkov, R., & Hadjipanayis, C. (2018). Magnetic hyperthermia therapy for the treatment of glioblastoma: a review of the therapy's history, efficacy and application in humans. *International Journal of Hyperthermia*, *34*(8), 1316–1328. https://doi.org/10.1080/02656736.2018.1430867

Mahmoudi, M., Sant, S., Wang, B., Laurent, S., & Sen, T. (2011). Superparamagnetic iron oxide nanoparticles (SPIONs): Development, surface modification and applications in chemotherapy. *Advanced Drug Delivery Reviews*, *63*(1–2), 24–46. https://doi.org/10.1016/j.addr.2010.05.006

Mahmoudi, M., Simchi, A., Imani, M., & Hafeli, U. O. (2009). Superparamagnetic iron oxide nanoparticles with rigid cross-linked polyethylene glycol fumarate coating for application in imaging and drug delivery. *Journal of Physical Chemistry C*, *113*(19), 8124–8131.

https://doi.org/10.1021/jp900798r

Mahmoudi, M., Simchi, A., Imani, M., Shokrgozar, M. A., Milani, A. S., Häfeli, U. O., & Stroeve, P. (2010). A new approach for the in vitro identification of the cytotoxicity of superparamagnetic iron oxide nanoparticles. *Colloids and Surfaces B: Biointerfaces*, *75*(1), 300–309. https://doi.org/10.1016/j.colsurfb.2009.08.044

Maity, D., & Agrawal, D. C. (2007). Synthesis of iron oxide nanoparticles under oxidizing environment and their stabilization in aqueous and non-aqueous media. *Journal of Magnetism and Magnetic Materials*, *308*(1), 46–55. https://doi.org/10.1016/j.jmmm.2006.05.001

Mascolo, M. C., Pei, Y., & Ring, T. A. (2013). Room Temperature Co-Precipitation Synthesis of Magnetite Nanoparticles in a Large ph Window with Different Bases. *Materials*, *6*(12), 5549–5567. https://doi.org/10.3390/ma6125549

McBain, S. C., Yiu, H. H. P., & Dobson, J. (2008). Magnetic nanoparticles for gene and drug delivery. *International Journal of Nanomedicine*, *3*(2), 169–180. https://doi.org/10.2147/ijn.s1608

Miller, K. J., Sofman, M., McNerny, K., & McHenry, M. E. (2010). Metastable γ -FeNi nanostructures with tunable Curie temperature. *Journal of Applied Physics*, *107*(9). https://doi.org/10.1063/1.3334198

Mizukoshi, Y., Shuto, T., Masahashi, N., & Tanabe, S. (2009). Preparation of superparamagnetic magnetite nanoparticles by reverse precipitation method: Contribution of sonochemically generated oxidants. *Ultrasonics Sonochemistry*, *16*(4), 525–531. https://doi.org/10.1016/j.ultsonch.2008.12.017

Mohapatra, M., & Anand, S. (2011). Synthesis and applications of nano-structured iron

oxides/hydroxides – a review. *International Journal of Engineering, Science and Technology*, *2*(8). https://doi.org/10.4314/ijest.v2i8.63846

Mondal J, Panigrahi AK, & Khuda-Bukhsh AR. (2014). Conventional Chemotherapy: Problems and Scope for Combined Therapies with Certain Herbal Products and Dietary Supplements. *Austin Journal of Cellular and Molecular Biology*, *1*(1), 0–10. www.austinpublishinggroup.com

Naji, A., Eitoku, M., Favier, B., Deschaseaux, F., Rouas-Freiss, N., & Suganuma, N. (2019). Biological functions of mesenchymal stem cells and clinical implications. *Cellular and Molecular Life Sciences*, *76*(17), 3323–3348. https://doi.org/10.1007/s00018-019-03125-1

Nasseri, M., Gahramanov, S., Netto, J. P., Fu, R., Muldoon, L. L., Varallyay, C., Hamilton, B. E., & Neuwelt, E. A. (2014). Evaluation of pseudoprogression in patients with glioblastoma multiforme using dynamic magnetic resonance imaging with ferumoxytol calls RANO criteria into question. *Neuro-Oncology*, *16*(8), 1146–1154. https://doi.org/10.1093/neuonc/not328

Nurdin, I., Ridwan, & Satriananda. (2016). The effect of pH and time on the stability of superparamagnetic maghemite nanoparticle suspensions. *MATEC Web of Conferences*, *39*. https://doi.org/10.1051/matecconf/20163901001

Pardoe, H., Chua-anusorn, W., St. Pierre, T. G., & Dobson, J. (2001). Structural and magnetic properties of nanoscale iron oxide particles synthesized in the presence of dextran or polyvinyl alcohol. *Journal of Magnetism and Magnetic Materials*, *225*(1–2), 41–46. https://doi.org/10.1016/S0304-8853(00)01226-9

Park, J., Lee, E., Hwang, N. M., Kang, M., Sung, C. K., Hwang, Y., Park, J. G., Noh, H. J., Kim, J. Y., Park, J. H., & Hyeon, T. (2005). One-nanometer-scale size-controlled

synthesis of monodisperse magnetic iron oxide nanoparticles. *Angewandte Chemie - International Edition*, *44*(19), 2872–2877. https://doi.org/10.1002/anie.200461665

Parkes, L. M., Hodgson, R., Lu, L. T., Tung, L. D., Robinson, I., Fernig, D. G., & Thanh, N. T. K. (2008). Cobalt nanoparticles as a novel magnetic resonance contrast agent - Relaxivities at 1.5 and 3 Tesla. *Contrast Media and Molecular Imaging*, *3*(4), 150–156. https://doi.org/10.1002/cmmi.241

Peng, X. H., Qian, X., Mao, H., Wang, A. Y., Chen, Z. G., Nie, S., & Shin, D. M. (2008). Targeted magnetic iron oxide nanoparticles for tumor imaging and therapy. *International Journal of Nanomedicine*, *3*(3), 311–321. https://doi.org/10.2147/ijn.s2824

Peng, Y. K., Tsang, S. C. E., & Chou, P. T. (2016). Chemical design of nanoprobes for T1-weighted magnetic resonance imaging. *Materials Today*, *19*(6), 336–348. https://doi.org/10.1016/j.mattod.2015.11.006

Perez De Berti, I. O., Cagnoli, M. V., Pecchi, G., Alessandrini, J. L., Stewart, S. J., Bengoa, J. F., & Marchetti, S. G. (2013). Alternative low-cost approach to the synthesis of magnetic iron oxide nanoparticles by thermal decomposition of organic precursors. *Nanotechnology*, *24*(17). https://doi.org/10.1088/0957-4484/24/17/175601

Petcharoen, K., & Sirivat, A. (2012). Synthesis and characterization of magnetite nanoparticles via the chemical co-precipitation method. *Materials Science and Engineering B: Solid-State Materials for Advanced Technology*, *177*(5), 421–427. https://doi.org/10.1016/j.mseb.2012.01.003

Ramanan, V. R. (2003). IEEE Transactions on Magnetics: Foreword. *IEEE Transactions on Magnetics*, *39*(5 II), 2219. https://doi.org/10.1109/TMAG.2003.817591

Regmi, R., Black, C., Sudakar, C., Keyes, P. H., Naik, R., Lawes, G., Vaishnava, P., Rablau,

C., Kahn, D., Lavoie, M., Garg, V. K., & Oliveira, A. C. (2009). Effects of fatty acid surfactants on the magnetic and magnetohydrodynamic properties of ferrofluids. *Journal of Applied Physics*, *106*(11). https://doi.org/10.1063/1.3259382

Rossi, L. M., Costa, N. J. S., Silva, F. P., & Wojcieszak, R. (2014). Magnetic nanomaterials in catalysis: Advanced catalysts for magnetic separation and beyond. *Green Chemistry*, *16*(6), 2906–2933. https://doi.org/10.1039/c4gc00164h

S., M., A., J., N., R., A.M., A., J., X., D., A., A., H., J.R., L., F., P.-B., S.C., S., R.J., M., X., C., N.R., S., & R.P., C. (2015). Molecular magnetic resonance imaging of angiogenesis in vivo using polyvalent cyclic RGD-iron oxide microparticle conjugates. *Theranostics*, *5*(5), 515–529. http://www.thno.org/%5Cnhttp://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed13&NEWS=N&AN=2015075858

Sarkar, S., Döring, A., Zemp, F. J., Silva, C., Lun, X., Wang, X., Kelly, J., Hader, W., Hamilton, M., Mercier, P., Dunn, J. F., Kinniburgh, D., Van Rooijen, N., Robbins, S., Forsyth, P., Cairncross, G., Weiss, S., & Yong, V. W. (2014). Therapeutic activation of macrophages and microglia to suppress brain tumor-initiating cells. *Nature Neuroscience*, *17*(1), 46–55. https://doi.org/10.1038/nn.3597

Shapira, A., Livney, Y. D., Broxterman, H. J., & Assaraf, Y. G. (2011). Nanomedicine for targeted cancer therapy: Towards the overcoming of drug resistance. *Drug Resistance Updates*, *14*(3), 150–163. https://doi.org/10.1016/j.drup.2011.01.003

Shevtsov, M. A., Nikolaev, B. P., Yakovleva, L. Y., Dobrodumov, A. V., Zhakhov, A. V., Mikhrina, A. L., Pitkin, E., Parr, M. A., Rolich, V. I., Simbircev, A. S., & Ischenko, A. M. (2015). Recombinant Interleukin-1 Receptor Antagonist Conjugated to Superparamagnetic Iron Oxide Nanoparticles for Theranostic Targeting of Experimental

Glioblastoma. *Neoplasia (United States)*, *17*(1), 32–42. https://doi.org/10.1016/j.neo.2014.11.001

Shi, Q., Pisani, L. J., Lee, Y. K., Messing, S., Ansari, C., Bhaumik, S., Lowery, L., Lee, B. D., Meyer, D. E., & Daldrup-Link, H. E. (2013). Evaluation of the novel USPIO GEH121333 for MR imaging of cancer immune responses. *Contrast Media and Molecular Imaging*, *8*(3), 281–288. https://doi.org/10.1002/cmmi.1526

Shuel, S. L. (2022). Targeted cancer therapies. *Canadian Family Physician*, *68*(7), 515–518. https://doi.org/10.46747/cfp.6807515

Soenen, S. J. H., & De Cuyper, M. (2009). Assessing cytotoxicity of (iron oxide-based) nanoparticles: An overview of different methods exemplified with cationic magnetoliposomes. *Contrast Media and Molecular Imaging*, *4*(5), 207–219. https://doi.org/10.1002/cmmi.282

Stanley, S. A., Gagner, J. E., Damanpour, S., Yoshida, M., Dordick, J. S., & Friedman, J. M. (2012). Radio-wave heating of iron oxide nanoparticles can regulate plasma glucose in mice. *Science*, *336*(6081), 604–608. https://doi.org/10.1126/science.1216753

Stoll, G., & Bendszus, M. (2010). New approaches to neuroimaging of central nervous system inflammation. *Current Opinion in Neurology*, *23*(3), 282–286. https://doi.org/10.1097/WCO.0b013e328337f4b5

Sugumaran, P. J., Liu, X. L., Herng, T. S., Peng, E., & Ding, J. (2019). GO-Functionalized Large Magnetic Iron Oxide Nanoparticles with Enhanced Colloidal Stability and Hyperthermia Performance. *ACS Applied Materials and Interfaces*. https://doi.org/10.1021/acsami.9b04261

Sun, C., Lee, J. S. H., & Zhang, M. (2008). Magnetic nanoparticles in MR imaging and drug

delivery. *Advanced Drug Delivery Reviews*, *60*(11), 1252–1265. https://doi.org/10.1016/j.addr.2008.03.018

Sun, S., & Zeng, H. (2002). Size-controlled synthesis of magnetite nanoparticles. *Journal of the American Chemical Society*, *124*(28), 8204–8205. https://doi.org/10.1021/ja026501x

Sun, S., Zeng, H., Robinson, D. B., Raoux, S., Rice, P. M., Wang, S. X., & Li, G. (2004). Monodisperse MFe2O4 (M = Fe, Co, Mn) Nanoparticles. *Journal of the American Chemical Society*, *126*(1), 273–279. https://doi.org/10.1021/ja0380852

Sun Y-P, Lia X-Q, Zhanga W-X, W. H. (2007). *Attarad Ali,1 Hira Zafar,1 Muhammad Zia,1 Ihsan ul Haq,2 Abdul Rehman Phull,3 Joham Sarfraz Ali,1 and Altaf Hussain*.

Taheri, S., Shah, N. J., & Rosenberg, G. A. (2016). Analysis of pharmacokinetics of Gd-DTPA for dynamic contrast-enhanced magnetic resonance imaging. *Magnetic Resonance Imaging*, *34*(7), 1034–1040. https://doi.org/10.1016/j.mri.2016.04.014

Taylor, A., Wilson, K. M., Murray, P., Fernig, D. G., & Lévy, R. (2012). Long-term tracking of cells using inorganic nanoparticles as contrast agents: Are we there yet? *Chemical Society Reviews*, *41*(7), 2707–2717. https://doi.org/10.1039/c2cs35031a

Townson, J. L., Ramadan, S. S., Simedrea, C., Rutt, B. K., MacDonald, I. C., Foster, P. J., & Chambers, A. F. (2009). Three-dimensional imaging and quantification of both solitary cells and metastases in whole mouse liver by magnetic resonance imaging. *Cancer Research*, *69*(21), 8326–8331. https://doi.org/10.1158/0008-5472.CAN-09-1496

Varallyay, C. G., Muldoon, L. L., Gahramanov, S., Wu, Y. J., Goodman, J. A., Li, X., Pike, M. M., & Neuwelt, E. A. (2009). Dynamic MRI using iron oxide nanoparticles to assess early vascular effects of antiangiogenic versus corticosteroid treatment in a glioma model. *Journal of Cerebral Blood Flow and Metabolism*, *29*(4), 853–860.

https://doi.org/10.1038/jcbfm.2008.162

Veiseh, O., Gunn, J. W., & Zhang, M. (2010). Design and fabrication of magnetic nanoparticles for targeted drug delivery and imaging. *Advanced Drug Delivery Reviews*, *62*(3), 284–304. https://doi.org/10.1016/j.addr.2009.11.002

Vereda, F., De Vicente, J., & Hidalgo-Álvarez, R. (2007). Influence of a magnetic field on the formation of magnetite particles via two precipitation methods. *Langmuir*, *23*(7), 3581–3589. https://doi.org/10.1021/la0633583

Wabler, M., Zhu, W., Hedayati, M., Attaluri, A., Zhou, H., Mihalic, J., Geyh, A., Deweese, T. L., Ivkov, R., & Artemov, D. (2014). Magnetic resonance imaging contrast of iron oxide nanoparticles developed for hyperthermia is dominated by iron content. *International Journal of Hyperthermia*, *30*(3), 192–200. https://doi.org/10.3109/02656736.2014.913321

Weber, W. A. (2006). Positron emission tomography as an imaging biomarker. *Journal of Clinical Oncology*, *24*(20), 3282–3292. https://doi.org/10.1200/JCO.2006.06.6068

WHO | World Health Organization. (n.d.). Retrieved May 31, 2022, from https://www.who.int/

Woo, K., Hong, J., Choi, S., Lee, H. W., Ahn, J. P., Kim, C. S., & Lee, S. W. (2004). Easy synthesis and magnetic properties of iron oxide nanoparticles. *Chemistry of Materials*, *16*(14), 2814–2818. https://doi.org/10.1021/cm049552x

Wu, W., He, Q., & Jiang, C. (2008). Magnetic iron oxide nanoparticles: Synthesis and surface functionalization strategies. *Nanoscale Research Letters*, *3*(11), 397–415. https://doi.org/10.1007/s11671-008-9174-9

Xia, T., Wang, J., Wu, C., Meng, F., Shi, Z., Lian, J., Feng, J., & Meng, J. (2012). Novel complex-coprecipitation route to form high quality triethanolamine-coated Fe 3O 4

nanocrystals: Their high saturation magnetizations and excellent water treatment properties. *CrystEngComm*, *14*(18), 5741–5744. https://doi.org/10.1039/c2ce25813g

Xu, J., Sun, J., Wang, Y., Sheng, J., Wang, F., & Sun, M. (2014). Application of iron magnetic nanoparticles in protein immobilization. *Molecules*, *19*(8), 11465–11486. https://doi.org/10.3390/molecules190811465

Xu, Z., Shen, C., Tian, Y., Shi, X., & Gao, H. J. (2010). Organic phase synthesis of monodisperse iron oxide nanocrystals using iron chloride as precursor. *Nanoscale*, *2*(6), 1027–1032. https://doi.org/10.1039/b9nr00400a

Yang, I., Han, S. J., Kaur, G., Crane, C., & Parsa, A. T. (2010). The role of microglia in central nervous system immunity and glioma immunology. *Journal of Clinical Neuroscience*, *17*(1), 6–10. https://doi.org/10.1016/j.jocn.2009.05.006

Yu, W. W., Falkner, J. C., Yavuz, C. T., & Colvin, V. L. (2004). Synthesis of monodisperse iron oxide nanocrystals by thermal decomposition of iron carboxylate salts. *Chemical Communications*, *20*, 2306–2307. https://doi.org/10.1039/b409601k

Zhu, H. (Nanjing C. (2011). *Targeted Nanoparticle Drug for Magnetic Hyperthermia Treatment on Malignant Tumors*. http://search.ebscohost.com/login.aspx?direct=true&db=edspap&AN=edspap.20110177153&site=eds-live

Zhu, N., Ji, H., Yu, P., Niu, J., Farooq, M. U., Akram, M. W., Udego, I. O., Li, H., & Niu, X. (2018). Surface modification of magnetic iron oxide nanoparticles. *Nanomaterials*, *8*(10). https://doi.org/10.3390/nano8100810

Zia, M., Phull, A. R., & Ali, J. S. (2016). Challenges of Iron Oxide Nanoparticles. *Powder Technology*, *7*(6), 49–67.

Zimmer, C., Wright, S. C., Engelhardt, R. T., Johnson, G. A., Kramm, C., Breakefield, X. O., & Weissleder, R. (1997). Tumor cell endocytosis imaging facilitates delineation of the glioma-brain interface. *Experimental Neurology*, *143*(1), 61–69. https://doi.org/10.1006/exnr.1996.6350