MAGNETIC NANOPARTICLES FOR HYPERTHERMIA: A PROMISING TOOL IN CANCER TREATMENT

Abstract

In the current chapter, we discuss about the various kinds of magnetic nanoparticles, their magnetic properties and their different modes of synthesis namely co-precipitation, Hydrothermal and green biosynthesis. Thereafter, we discuss the various applications of magnetic nanoparticles with special emphasis on biomedical applications specially hyperthermia-based therapy in cancer cells using magnetic nanoparticles. We finally end the chapter by discussing the toxicity, biodistribution pattern and pharmacokinetic properties of the magnetic nanoparticles. Magnetic induced Hyperthermia is an active and pertinent area of research now which is slowly gaining prominence but it still suffers from various limitations and hence have not yet been properly utilized in therapeutic approaches. Hence, more research is needed to make it more accessible for therapeutic applications in near future and truly reach its translation potential in several therapies of cancer.

Keywords-Magnetic Nanoparticles, Hyperthermia, Cancer Therapy, Photodynamic Therapy, Green Biosynthesis

Authors

Subhabrata Guha
Department of Signal Transduction and Biogenic Amines
Chittaranjan National Cancer Institute
Kolkata, India
subhabrataguha.zoo@gmail.com

Rimi Mukherjee
Department of Signal Transduction and Biogenic Amines
Chittaranjan National Cancer Institute
Kolkata, India
rimi.mukrimi@gmail.com

Debojit Talukdar
Department of Signal Transduction and Biogenic Amines
Chittaranjan National Cancer Institute
Kolkata, India
debojit1095@gmail.com

Dr. Nabendu Murmu
Department of Signal Transduction and Biogenic Amines
Chittaranjan National Cancer Institute
Kolkata, India
nabendu.murmu@cnci.ac.in

Dr. Gaurav Das
Department of Signal Transduction and Biogenic Amines
Chittaranjan National Cancer Institute
Kolkata, India
biotechgaurav70@gmail.com

I. INTRODUCTION

Nowadays times, Cancer is the second most leading cause of mortality globally after the heart disease [1]. It is characterized by the uncontrolled and irregular cellular proliferation, caused by either the genetic lesions in any gene or the somatic mutations in upstream cell signaling pathways, resulting in formation of tumor [2].However, this tumor are categorized into two distinct groups, one is benign while the other is malignant tumor. Benign tumor is actually considered as localized tumor that means they are confined to a specific region and don't spread to other tissues or organs whereas malignant tumor have that potential to spread throughout the body i.e. they possess metastatic potential [3]. Due to their metastatic ability, recurrence, heterogeneity and resistance to radiotherapy, chemotherapy and hormonal therapy; various traditional approaches become ineffective against many malignancies [4]. Moreover, the malignant tumors also have the ability to avoid immune responses which is one of the exact reasons for failing the conventional therapeutic approaches. Among all the conventional therapeutic approaches, chemotherapy is most predominantly used option for various cancer treatments. But there are certain restrictions and limitations of the chemotherapeutic agents such as the nonspecific distribution, poor bioavailability, relatively poor solubility in body fluids and the rapid blood clearance [5], [6].Due to these factors, restrictions and limitations the ultimate goal of cancer therapy i.e. selectively destroyed the cancer cells without affecting the adjacent healthy and normal cells or tissues which have not fulfilled till now. Scientists, are now a days trying to introduce new approaches like hyperthermic treatment which can synergistically act with the conventional approaches to make a completely new model in cancer therapy.

Basically, hyperthermic treatment is considered as heating the tumor cells at 40-45° C to destroy the tumor cells, inducing a series of thermally induced metabolic activities such as apoptosis, leading to subsequent cell death [7]. All the events related to hyperthermia results to alter the extracellular microenvironment, stimulating immune responses which provide the tumor cells an anaerobic metabolic scheme [8]. There are different types of hyperthermic treatment present based on their site of application such as: whole body hyperthermia, regional hyperthermia and localized hyperthermia. Whole body hyperthermia is classified into two distinct methods i.e. invasive method and non-invasive method based on the mode of application. In invasive whole body hyperthermia method, heating blood extra corporeally whereas in non-invasive whole body hyperthermia method, increasing the temperature using hot air, hot wax, radiofrequency (RF) or infra-red (IR) irradiation but this method can't be useful for deep tumor treatment [9]. Regional hyperthermia also includes two different approaches i.e. invasive and non-invasive approach. In invasive regional hyperthermia approach, tumors are heated by the thermal conduction or using the magnetic implants, whereas in non-invasive regional hyperthermia approach, non-ionizing electromagnetic radiation (EMR) or ultrasound are used to generate heat [10]. In localized hyperthermia, small tumors depth up to 4 cm. are heated and destroyed by either the invasive or the non-invasive methods [10].

While destroying a huge quantity of tumor cells with high temperatures, normal cells are also severely damaged non-specifically in a conventional hyperthermia treatment. Thus, magnetic nanoparticles (MNPs) mediated intracellular hyperthermia is developed which has the ability to overcome this problem [11]. The main purpose of using magnetic nanoparticles for the hyperthermia treatment is to generate the heat in a controlled manner and destroy only

the tumor cells specifically. It is based on the principle of converting the magnetic energy into heat energy in the oscillating magnetic field [12]. Besides that, another reason for choosing the magnetic nanoparticles (MNPs) is that they are non-toxic in nature [13].

In this book chapter, we tried to focus on different types, criteria, developments, applications of magnetic nanoparticles (MNPs) based hyperthermic treatment, which is the most advanced, futuristic and potential approach for cancer treatment.

II. MAGNETIC NANOPARTICLES

The most accessible types of treatment adapted for cancer patients nowadays have been chemotherapy, surgery and radiotherapy. Magnetic Hyperthermia has been known to the clinicians and scientists for over a decade yet it is still not prevalently used. Even the real use of nanoparticles is a rare sight even in today's world. However, because of its unique size as well as the physicochemical properties it possesses, nanoparticles are highly advantageous. Because of the widespread application of magnetic nanoparticles, an emphasis should be given to its types and means of its production [14]. In order to utilize the magnetic nanoparticles hence produced in medical field, they should be stable at physiological pH in an aqueous medium. The nanoparticles should be small enough so that they do not precipitate while they are inside the system avoiding vessel embolism. They should also be stable depending on the surface chemistry and charge distribution on it. After synthesis, the nanoparticles should be enclosed in a bio-compatible polymer to prevent agglomeration and degradation upon exposure to the biological system. This encapsulation will also ensure proper binding of the MNPs to the suitable receptors. Shrinkage of tumors can easily be addressed with the advent of Nano-magnetic hyperthermia. The biggest advantage of these particles is that due to its size they can be easily accommodated in a minor space creating a difference in the temperature profiles of the cancerous and a normal healthy tissue [15]. In medical science, magnetite which is iron oxide nanoparticles (Fe_3O_4) or maghemite (γ-Fe_2O_3) are most commonly used [16].

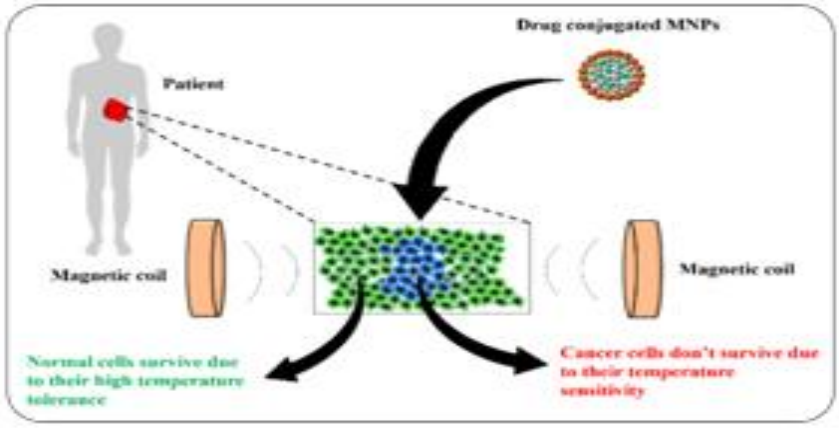

Figure 1: Pictorial representation of therapeutic approach of MNPs induced Hyperthermia (MIH) model

The use of magnetic nanoparticles in treatments of cancer is based on the principle that tumors are composed of heterogeneous tissues comprising of necrosis in an acidic and

hypoxic tumor microenvironment. Cells prevalent in these regions are usually immune to cytostatic or pro-apoptotic drugs but the acidotic and hypoxic tumor tissue is susceptible to heat than the adjoining normal healthy tissues. As a response to enhanced temperature due to magnetic hyperthermia, there is a possibility of increased vascularization stimulating an escalation of oxygen level thereby making the cells sensitive to these aforementioned class of drugs [17]. Tumor cells in the S-phase of cell cycle i.e. those cells that are undergoing DNA replication are specifically unperturbed by ionizing radiation but sensitive to an increased temperature. Thus, if tumor cells resistant to an ionizing radiation are exposed to an increased temperature of about 42°C for a considerable amount of time, it will impart some cytotoxic effect to these cells [18]. This effect due to an elevated temperature is mostly pronounced in large tumors having a reduced flow to the central region of the tumor along with having a lower surface to volume ratio due to which there is negligible loss of heat by thermal diffusion.

An ideal magnetic nanoparticle should be efficient but safe to use at the same time. It works on the basic principle of energy conversion from electromagnetic to thermal. In order to elicit the therapeutic efficacies of the synthesized magnetic nanoparticles, this thermal energy conversion efficiency needs to be improved by several folds. In presence of an alternating magnetic field, this heating effect can be regulated by various agents like eddy current, natural resonance, hysteresis and relaxation effects and so on. The size of the magnetic nanoparticles employed in magnetic hyperthermia usually ranges from 1 to 200 nm. Ferromagnetic substances are most widely used for this purpose which when placed in a magnetic field produces a dipole as shown in **Figure 1**. Certain nanoparticles are susceptible to oxidation and aggregation hence needs to be protected by some coating (organic or inorganic) [19].

Owing to their small size, they possess an advantage of better diffusion and distribution to the target sites. Since these magnetic nanoparticles can be easily manipulated by an externally applied magnetic field, there is a wide range of application for these like in biology and medicine like cell labelling, drug delivery and MRI (Magnetic Resonance Imaging) [20].

1. **Magnetic properties of magnetic nanoparticles:** Movements of particles brought about by electrons, protons and positive and negative ions having mass and electric charges are responsible for magnetic effects. Any electric charge carrying particle having a spin is responsible for a magnetic dipole which is known as magneton. Magnetic moments and its direction are a measure of the various forms of magnetism prevalent in nature. Basic types of magnetism are: Ferromagnetism, Ferrimagnetism, Anti-ferromagnetism, Diamagnetism and Paramagnetism [21].

2. **Types of magnetic nanoparticles:** Based on the structure, magnetic nanoparticles are classified into two large groups such as Magnetic Metal Oxide Nanoparticles (MMONPs) and Magnetic Alloy Nanoparticles (MANPs). In **Table 1,** few therapeutic agents under MMONPs and MANPs are shortlisted and their applications and pros and cons are thoroughly discussed.

Table 1: List of various types of Magnetic Nanoparticles (MNPs), their applications and advantages-disadvantages

MNPs Classification	Therapeutic agents	Advantages & Disadvantages	Applications	References
Magnetic Metal Oxide Nanoparticles (MMONPs)	Mn Fe_2O_4	Physicochemical performance	Drug delivery	[16], [22]
	NiO	High magnetic permeability	Magnetic hyperthermia, inhibition of biofilm formation	
	$CoFe_2O_4$	Colloidal stability	Gene therapy	
	$NiFe_2O_4$	Low toxicity	MRI	
	Co_3O_4	Super-paramagnetism	Electromagnetic and optical devices	
		Large surface area to volume ratio	Bio-sensing and batteries	
	Fe_3O_4	High saturation magnetization	Labelling cells	[23]
	γ-Fe_2O_3	High magnetic susceptibility	MRI Contrast agents	
Magnetic Alloy Nanoparticles (MMONPs)	Co-Ni	High coercivity and resistance against oxidation	Biomedicine, Hyperthermia treatment	[24]
	Fe-Co	Large magnetic anisotropy	Ultra high-density Magnetic recording media	
	Fe-Pt	High magnetic moment	Magnetic storage	[25]
	Fe-Ni	Narrow size distribution	Ultra high-density Magnetic recording media	

3. **Synthesis of magnetic nanoparticles in case of hyperthermia:** In the last decade, there have been ample publications about various Magnetic Nanoparticles and their various synthesis protocols achieving stable, shape-controlled and minute magnetic nanoparticles. The most common methods adapted for their synthesis are microemulsion, thermal decomposition, laser pyrolysis, co-precipitation, solvothermal, carbon arc, combustion synthesis, microwave assisted, sonochemical, chemical vapour decomposition and green synthesis etc. Physical methods can also be adapted for synthesis of magnetic nanoparticles like mechanical milling, gas phase deposition, electron beam lithography, vapour deposition and patterning, electrical explosion of wires etc.

    - **Co-Precipitation:** In this process usually one or more particulates are separated from the solvent where they are otherwise soluble - mainly by the process of grain growth or nucleation. Since the precursors required in this process are less toxic, it is mostly used in biology and medicine. It requires the involvement of a salt and a base

ultimately producing insoluble solid particles in presence or absence of any precipitating agent [26]. From this method, magnetic nanoparticles of various shapes and sizes can be synthesized even at room temperature. Based on the ionic strength, pH, ratio of ions and the type of salt used in the solution, different shapes and sizes of the magnetic nanoparticles are obtained. An ideal pH for this should be 8 to 14. With an increase of these two aforementioned factors, the size of the magnetic nanoparticles gradually decreases [27].

The reaction is as follows: $Fe^{2+} + 2OH^- \rightarrow Fe(OH)_2$

$$Fe^{3+} + 3OH^- \rightarrow Fe(OH)_3$$

$$Fe(OH)_2 + 2Fe(OH)_3 \rightarrow Fe_3O_4 + 4H_2O$$

This is a bottom-up approach where salts are engaged which will produce particles that will undergo nucleation.

- **Hydrothermal:** The hydrothermal/solvothermal method of magnetic nanoparticle preparation is mostly used to produce metals and oxides. This involves formation of crystals which are usually of a larger diameter placed in a sealed container. The solution is heated at a considerable high temperature and pressure of around 130-250°C and 0.3-4.0 MPa respectively [28]. The substrates in this reaction are namely iron carbonyls and acetylacetonates. However, it should be noted that the magnetic nanoparticles that are obtained by this process have to be purified before it can meet the biomedical demands.

- **Green Biosynthesis:** Using this process, magnetic nanoparticles are produced without any toxic or hazardous by-products. This is an eco-friendly process that is least detrimental to the environment or human health. The physical or chemical methods of magnetic nanoparticle production has a much higher yield and the particles produced are of various morphology and size but these processes are expensive whereas this process is simple and much more economical [29].

  This is a “bottom up” method where the metal atoms aggregate to form clusters that further leads to the formation of magnetic nanoparticles. The biological compound that is being used here can act as a capping agent in some cases in addition to a reducing agent. In this process, the substrates that are involved are a metal salt and the biological compound like a leaf or fruit extract. There have been reports of Fe_3O_4 nanoparticles being synthesized by green synthesis which is non-toxic with an elevated level of bioavailability. The magnetic nanoparticles thus obtained can also be conjugated with an enzyme or a drug with an aim to increase the overall efficacy and applicability. In presence of an external magnetic field or if exposed to heating by the effect of an alternating magnetic field, they can be used in hyperthermia treatment [30].

4. **Recent studies and application of magnetic nanoparticles:** Magnetic nanoparticles possess a variety of biomedical applications as listed in **Figure 2**, whose classification can be made based on their applications *in vivo* and *in vitro*. *In vitro* applications are mostly associated with the diagnostic separation, selection and magneto-relaxometry, while on the other hand *in vivo* applications are mostly involved in therapeutic such as

hyperthermia, drug-targeting as well as for diagnostic applications like nuclear magnetic resonance (NMR) imaging and Magnetic Resonance Imaging (MRI) [31]–[33].

The *in vivo* as well as *in vitro* use of these magnetic nanoparticles is guided by two major factors which includes the size and surface functionality. For example, Super Paramagnetic Iron Oxide Nanoparticles (SPIOs) have their distribution property dependent on their diameter even without targeting surface ligands. For proper distribution in the body through the blood and lymph circulation and passing through the finest capillary walls, particles having a diameter size ranging from 10 to less than 40 nm like ultra-small SPIOs, are of great importance [34].

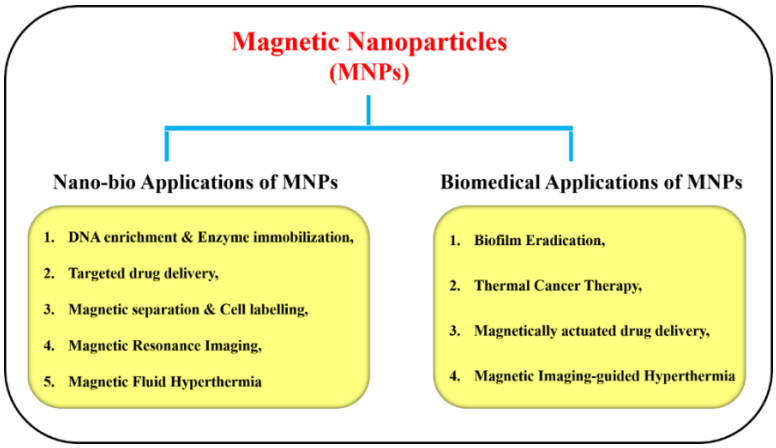

Figure 2: Different Nano-bio and Biomedical Applications of Magnetic Nanoparticles

- **Magnetic Nanoparticles based Hyperthermia Treatment:** When a superparamagnetic iron oxide for example is positioned between an alternating magnetic field generated using Alternating current (AC), the direction of magnetization instantly flips its orientation (between parallel and antiparallel) allowing the simultaneous conversion of energy from magnetic to heat. This magnetic to heat energy transformation can be utilized for elevating the temperature of the tumor tissue to induce killing of these tumor cells using hyperthermic treatment as a killing strategy, as because the tumor cells are more susceptible to elevated temperature than their normal counterparts [35]. In previous studies the use of magnetite cationic liposomal nanoparticles and dextran coated magnetite nanoparticles are found to be efficient in elevating the temperature of the malignant cells in the tumor mass resulting in hyperthermia within the tissue, which may be considered as an efficient strategy for successful cancer therapy in our near future [36]. One noteworthy advantage of magnetic hyperthermia lies in the fact that the heat remains mainly restricted to the tumor region. As because of the fact that the amount of power absorbed by the nanoparticle is intensively size and shape dependent, therefore to control the temperature rigorously synthetic routes that are well defined and capable of producing uniform nanoparticles is required for which the utilization of nanometer-sized sub-domain magnetic particles is given more preference instead of multi-domain (micron-sized) particles [37], [38]. Magnetic hyperthermia is mainly involved in the controlled release of cytotoxic substances using a coating made of

heat labile material which is responsible to cause cell death through apoptotic as well as necrotic pathway [39]. Moreover, the effect of MNPs induced hyperthermia can be enhanced by conjugation of antibodies with the specific MNPs due to the anticancer effect possessed by the antibodies and also the selectivity towards cancer cells.Examples include MNPs which are anti-FGFR1 aptamer-tagged (for having an enhanced magnetic hyperthermia) and antibody-conjugated MNPs for robust anti-cancer effects of Cryptotanshinone [40], [41]. Combination of chemotherapy along with magnetic hyperthermia have been found to have enhanced tumor regression ability [42]. Apart from direct killing of cancer cells MNPs-MH also have the potential to generate antitumor immune response against the released tumor antigens and endogenous adjuvants **(**such as HSPs and DAMPs), which indicates the potential towards tumor therapy [26], [27]. Studies on the understanding of the hyperthermia induced anti-tumor immunity, suggested two possible mechanisms for antigen presentation guided by the over-expression of HSPs specially HSP 70 during hyperthermia as shown in **Figure 3** [45]. One of the possible mechanisms involve enhanced tumor antigen presentation through Class I MHC complex due to hyperthermia subsequently causing enhanced tumor immunogenicity. A model named "Relay-line model" was proposed for protein transfer during HSP mediated antigen presentation [46].

- The peptides are firstly carried to the endoplasmic reticulum through binding with the HSPs mainly HSP 70 and HSP 90 guided by the Transport Associated with Antigen processing (TAP) proteins.
- Then the transfer of peptides to gp 96 in the lumen of the ER takes place followed by the transfer of peptides from gp 96 to the MHC class I - β 2 micro-globulin complexes.

HSP 70 is known to augment the MHC class-I antigen expression on the surface of tumor cells leading to immune activation. Expression of HSP 70 is found to reach maximum around 24 h following the hyperthermic treatment whereas on augmentation of the expression of MHC class I molecules is associated with a slower response curve due to the fact that starting took place 24 h after heating and peaked around 48 h [45]. The other mechanism involved in the recognition of tumor antigens include the strategy of cross-presentation by the professional Antigen Presenting Cells (APCs). Other than the uptake of HSP - peptide complex through receptor mediated endocytosis, HSP has the potential of APC activation directly through monocyte based cytokine secretion and dendritic cells (DCs) maturation [45]. In summary, current evidence led to the speculation that hyperthermia based system has the potential to induce robust anti-tumor immune response. The increase in temperature above 43°C results in the induction of necrotic tumor cell death, leading to the production of a lot of HSPs, resulting in robust anti-tumor immunity [11]. The mechanism by which MNPs are responsible for causing cellular death of cancer cells can be analyzed by studying the mechanism of heat dissipation by MNPs. The dissipation of heat takes place mainly through two processes namely Neel and Brownian relaxation. Neel relaxation involves the reorientation of the magnetic moment in parallel with the applied magnetic field whereas Brownian relaxation on the other hand involves the rotation of the nanoparticle mechanically as a whole towards the applied magnetic field [47], [48]. When the alternating magnetic field

(AMF) is applied, the shear forces developed by the MNPs due to the Brownian relaxation can potentially cause lysis of the cells and release the lysosomal Cathepsins [49]. Moreover the tumor tissues are speculated to have an impaired mechanism of cooling which can be attributed to the altered vascular permeability in comparison to the normal tissues, which in turn may also be responsible for lysosomal permeability and Cell death [50].

- **Photothermal ablation:** This mode of therapy utilizes gold coated MNPs along with NIR or Visible laser light source which is responsible for production of thermal heat through electromagnetic photon absorption eventually causing cell death[51].

- **Photodynamic therapy (PDT):** This method involves the utilization of a photosensitizing agent which is responsible for generating singlet oxygen ($^1O_2$) guided by the use of an external light source for causing excitation resulting in free radical induced damage to cancer cells within a periphery of about 20 nm. [44], [45]. The conjugation of these agents to MNPs results in enhancement of the therapeutic efficacy and potential [52].

- **Drug delivery:** Drug targeting using Magnetic nanoparticles have emerged as one of the recent strategies for drug delivery [53]. For efficient magnetic drug targeting combining MNPs external magnetic field and/or magnetisable implants and fixing them at the local site following which the release of medication takes place and acts in the local region [54]. When transportation of drugs takes place at a specific site, it can effectively eliminate the possible side effects consequently reducing the required dosage. Surface modification of these particles by using various inorganic metals and organic polymers along with their oxides are done to make them biocompatible in addition to the attachment of various bioactive molecules for further functionalization [48], [49]. The competition involved between the forces acting on the particles by the blood compartment and the magnetic forces generated due to the magnet is actually responsible for guiding the drug localization using magnetic drug delivery system [55].

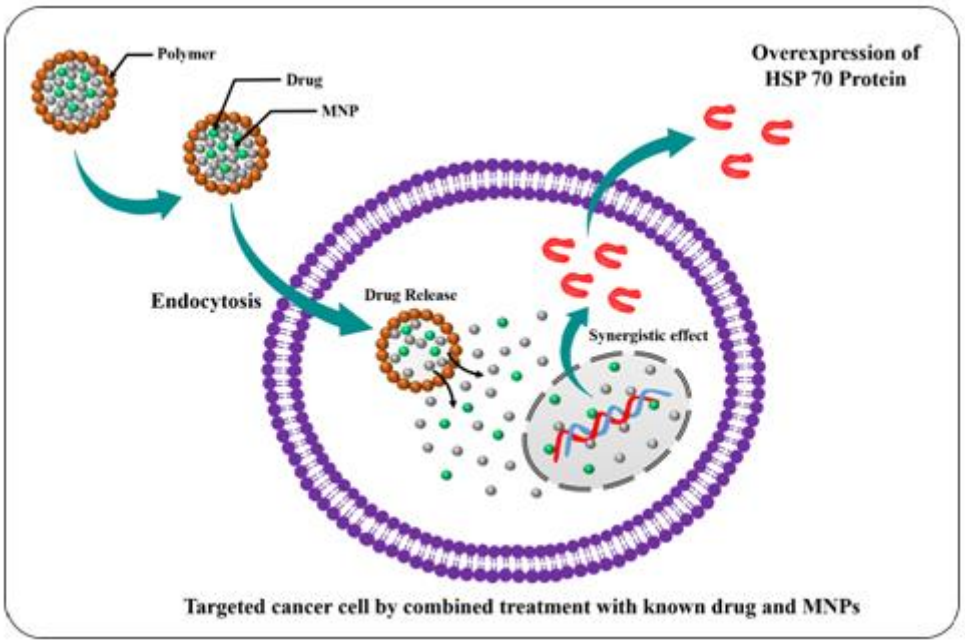

Figure 3: Pictorial representation of targeted cancer therapy with known drugs and Magnetic Nanoparticles in MNPs induced Hyperthermia (MIH) model

- **Radiotherapeutics:** Researches on Nanoparticles are being carried out to study their applications in the delivery of radionuclides and /or radio sensitizers responsible for inducing DNA damage in the cancer cells as a result of generating free radicals or ionic radiation [56]–[58]. Unique advantages are offered by MNPs over current radio therapeutic strategies by reducing the chances of off-target tissue damage due to the result of non-specific nature of the treatment. Moreover combined treatment along with chemotherapy or gene therapy has also been applied to study the effect of synergistic action [56].

III. TOXICITY, BIO-DISTRIBUTION, PHARMACOKINETICS

For successful application in the clinics there are three crucial parameters that needs to be studied which includes Toxicity, Pharmacokinetics and Bio-distribution. The pharmacokinetics and pharmacodynamics of the MNPs inside the body are governed by various parameters which includes hydrodynamic size, surface potential, coating, interaction of NPs with reticuloendothelial system (RES) [57]. Size of the MNPs also have a very crucial role in the excretion of the nanoparticles. Small sizes MNPs takes up the renal route for excretion, whereas the larger ones are taken up by the liver and spleen to eventually degrade and excrete them thorough the hepatobiliary route [58]. Physicochemical properties of the nanomaterials including size, structure, composition, surface charge, and surface modification provide a major contribution for the toxic nature of developed magnetic nanoparticle (MNP) formulations [59]–[61]. NPs having a neutral surface charge are found to possess a longer circulation time in comparison to the nanoparticles with either positive or negative charges on their surface [61]. Presence of Surface coating has been found to demonstrate important role in governing the circulation of MNPs. Therefore, careful manipulation of the circulation of the MNPs that significant in affecting the bio-distribution and biocompatibility of the MNPs

[62] as because its localization in certain organs like spleen and liver increase the risk of off-target toxicity. Other than the already mentioned parameters like size, surface charge, purity, bio-distribution, synthesis procedure and pharmacokinetic properties also plays a very important role in determining *in vivo* toxicity [63]. There are various mechanisms by which MNPs display toxicity which includes the Reactive oxygen species (ROS) generation by Fenton reaction; production of ROS directly from the surface of nanoparticles; affecting various signaling pathways ultimately resulting in the alteration in the functioning of mitochondria and other organelles. Due all these reasons, it's very crucial to assess and analyze the MNPs toxicity before they are being used in cancer therapy and diagnosis [64]–[66]. Causing cell death *in vitro* [67] by the generation of ROS was shown by use of either Uncoated or else dextran-coated superparamagnetic iron oxide nanoparticles (SPION) where SPION plays the source of ROS [68], [69]. However the extent to which generation of ROS takes place and cell death is caused depends on the cell type [70]. Adsorption of plasma proteins within a biologically relevant environment including albumins, complement system components, immunoglobulins by the nanoparticles similar to opsonization results in the protein corona formation which has the potential in promoting receptor-mediated phagocytosis, mitigating the function of active targeting agents, and also in altering key magnetic properties that includes degree of magnetization saturation. The resident macrophages take up these NPs mostly through phagocytosis in liver, kidney, spleen, and lymph nodes resulting in the sequestration of these nanoparticles and eventually clearance from the circulation [71]–[76]. Complication in MNP toxicity *in vivo* takes place more due to rapid protein adsorption on MNP surface accompanied by the protein corona formation on introducing into biological media, nano-bio interface along with its biological interactions [77]. Physicochemical properties of MNPs such as larger hydrodynamic size higher surface area to volume, negative surface charge, hydrophobicity is further responsible for governing the protein corona formation by independently showing protein adsorption [78]. Modifications of the MNP surfaces can be done for enhancing both passive [79] and active [80] accumulation while taking into consideration of the acute overloading of iron in a localized environment responsible for causing toxic effects [81], [82]. Moreover change in protein conformation upon adsorption or MNPs aggregation may end up in triggering cellular responses which may have unintended, adverse outcomes [83]. Surface coating of nanoparticles using materials such as polyethylene glycol (PEG) [84]–[86] polysaccharides [87] and zwitterions [88], [89] have shown reducing protein adsorption and also subsequently increasing circulation time in several investigations. One of the dominant strategy till date is PEGylation which is responsible for increasing the circulation time in magnetic particle imaging (MPI), which involves the application of both static and alternating magnetic fields on the subject in such a manner that measurement of a small volume of interest, the field-free point, containing the MNP tracer can be directly made without any background from weakly magnetized materials [90].

IV. CHALLENGES AND FUTURE PERSPECTIVES

Magnetic Induced Hyperthermia (MIH) remains an active area of research, but the technology remains still at its infancy with its several aspects remains yet to be explored. There are several challenges that needs to be overcome to open a new arena of nanotechnology and unlocking a wide range of future perspectives. Cancer treatment strategies face the most important challenge due to the large variety and heterogeneity that exists within various types of cancer. So, MIH that facilitates the destruction of secondary

tumors only, the problem of recurrence remains same. Therefore, for the development of complete curative treatment, strategies must be figured out to prevent the metastasis and recurrence. One of the root cause of cancer metastasis and recurrence involves the role of Cancer Stem cells (CSC) and efficient strategies involving MIH targeting CSC populations may open a new dimension in cancer therapy [7].

V. AUTHOR'S CONTRIBUTION

G.D and N.M conceptualized the whole manuscript, S.G, R.M and D.T wrote the manuscript, S.G drew all the diagrammatic images, R.M and D.T made all the charts and tables. Finally, all the authors read and approved the final submitted version of the manuscript.

VI. ACKNOWLEDGEMENTS

S.G and G.D acknowledge DST-INSPIRE Faculty Project (Ref No. DST/INSPIRE/04/2020/001299) for their fellowship and the research grant. R.M acknowledges Chittaranjan National Cancer Institute for her Institute fellowship, D.T acknowledges UGC for his JRF fellowship. All the authors acknowledge Dr. Jayanta Chakrabarti, Director, Chittaranjan National Cancer Institute, Kolkata for providing infrastructure for carrying out the work.

Conflict of Interest The authors declared that there is no conflict of interest.

REFERENCES

[1] E. B. Yahya and A. M. Alqadhi, "Recent trends in cancer therapy: A review on the current state of gene delivery," *Life Sci.*, vol. 269, p. 119087, Mar. 2021, doi: 10.1016/j.lfs.2021.119087.
[2] Z. Shen, J. Song, B. C. Yung, Z. Zhou, A. Wu, and X. Chen, "Emerging Strategies of Cancer Therapy Based on Ferroptosis," *Adv. Mater.*, vol. 30, no. 12, p. 1704007, 2018, doi: 10.1002/adma.201704007.
[3] C. E. Irish *et al.*, "Thermoradiotherapy for persistent cancer in previously irradiated fields," *Cancer*, vol. 57, no. 12, pp. 2275–2279, 1986, doi: 10.1002/1097-0142(19860615)57:12<2275::AID-CNCR2820571207>3.0.CO;2-B.
[4] Y. Sun, "Translational Horizons in the Tumor Microenvironment: Harnessing Breakthroughs and Targeting Cures," *Med. Res. Rev.*, vol. 35, no. 2, 2015, doi: 10.1002/med.21338.
[5] K. Cho, X. Wang, S. Nie, Z. G. Chen, and D. M. Shin, "Therapeutic nanoparticles for drug delivery in cancer," *Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res.*, vol. 14, no. 5, pp. 1310–1316, Mar. 2008, doi: 10.1158/1078-0432.CCR-07-1441.
[6] K. Han *et al.*, "Synergistic gene and drug tumor therapy using a chimeric peptide," *Biomaterials*, vol. 34, no. 19, pp. 4680–4689, Jun. 2013, doi: 10.1016/j.biomaterials.2013.03.010.
[7] J. Jose *et al.*, "Magnetic nanoparticles for hyperthermia in cancer treatment: an emerging tool," *Environ. Sci. Pollut. Res.*, vol. 27, no. 16, pp. 19214–19225, Jun. 2020, doi: 10.1007/s11356-019-07231-2.
[8] D. K. Chatterjee, P. Diagaradjane, and S. Krishnan, "Nanoparticle-mediated hyperthermia in cancer therapy," *Ther. Deliv.*, vol. 2, no. 8, pp. 1001–1014, Aug. 2011, doi: 10.4155/tde.11.72.
[9] A. J. Milligan, "Whole-body hyperthermia induction techniques," *Cancer Res.*, vol. 44, no. 10 Suppl, pp. 4869s–4872s, Oct. 1984.
[10] P. Wust *et al.*, "Hyperthermia in combined treatment of cancer," *Lancet Oncol.*, vol. 3, no. 8, pp. 487–497, Aug. 2002, doi: 10.1016/S1470-2045(02)00818-5.

[11] T. Kobayashi, "Cancer hyperthermia using magnetic nanoparticles," *Biotechnol. J.*, vol. 6, no. 11, pp. 1342–1347, Nov. 2011, doi: 10.1002/biot.201100045.
[12] X. Wu, Y. Tan, H. Mao, and M. Zhang, "Toxic effects of iron oxide nanoparticles on human umbilical vein endothelial cells," *Int. J. Nanomedicine*, vol. 5, pp. 385–399, 2010.
[13] Q. A. Pankhurst, J. Connolly, S. K. Jones, and J. Dobson, "Applications of magnetic nanoparticles in biomedicine," *J. Phys. Appl. Phys.*, vol. 36, no. 13, pp. R167–R181, Jun. 2003, doi: 10.1088/0022-3727/36/13/201.
[14] M. Peiravi, H. Eslami, M. Ansari, and H. Zare-Zardini, "Magnetic hyperthermia: Potentials and limitations," *J. Indian Chem. Soc.*, vol. 99, no. 1, p. 100269, Jan. 2022, doi: 10.1016/j.jics.2021.100269.
[15] J. Beik *et al.*, "Nanotechnology in hyperthermia cancer therapy: From fundamental principles to advanced applications," *J. Controlled Release*, vol. 235, pp. 205–221, Aug. 2016, doi: 10.1016/j.jconrel.2016.05.062.
[16] P. Tartaj, M. a del P. Morales, S. Veintemillas-Verdaguer, T. Gonz lez-Carre o, and C. J. Serna, "The preparation of magnetic nanoparticles for applications in biomedicine," *J. Phys. Appl. Phys.*, vol. 36, no. 13, pp. R182–R197, Jul. 2003, doi: 10.1088/0022-3727/36/13/202.
[17] A. J. Giustini, A. A. Petryk, S. M. Cassim, J. A. Tate, I. Baker, and P. J. Hoopes, "MAGNETIC NANOPARTICLE HYPERTHERMIA IN CANCER TREATMENT," *Nano LIFE*, vol. 01, no. 01n02, pp. 17–32, Mar. 2010, doi: 10.1142/S1793984410000067.
[18] J. D. Doss and C. W. McCabe, "A technique for localized heating in tissue: an adjunct to tumor therapy," *Med. Instrum.*, vol. 10, no. 1, pp. 16–21, Feb. 1976.
[19] M. K. Yazdi *et al.*, "16 - Magnetic nanoparticles in cancer therapy," in *Magnetic Nanoparticle-Based Hybrid Materials*, A. Ehrmann, T. A. Nguyen, M. Ahmadi, A. Farmani, and P. Nguyen-Tri, Eds. Woodhead Publishing, 2021, pp. 425–445. doi: 10.1016/B978-0-12-823688-8.00025-9.
[20] Z. R. Stephen, F. M. Kievit, and M. Zhang, "Magnetite nanoparticles for medical MR imaging," *Mater. Today*, vol. 14, no. 7–8, pp. 330–338, Jul. 2011, doi: 10.1016/S1369-7021(11)70163-8.
[21] "Magnetic Properties," *Chemistry LibreTexts*, Oct. 02, 2013. https://chem.libretexts.org/Bookshelves/Physical_and_Theoretical_Chemistry_Textbook_Maps/Supplemental_Modules_(Physical_and_Theoretical_Chemistry)/Physical_Properties_of_Matter/Atomic_and_Molecular_Properties/Magnetic_Properties (accessed Aug. 30, 2022).
[22] S. Saleem, B. Ahmed, M. S. Khan, M. Al-Shaeri, and J. Musarrat, "Inhibition of growth and biofilm formation of clinical bacterial isolates by NiO nanoparticles synthesized from Eucalyptus globulus plants," *Microb. Pathog.*, vol. 111, pp. 375–387, Oct. 2017, doi: 10.1016/j.micpath.2017.09.019.
[23] N. P. Herring *et al.*, "Microwave Synthesis of Metal Oxide Nanoparticles," in *Metal Oxide Nanomaterials for Chemical Sensors*, M. A. Carpenter, S. Mathur, and A. Kolmakov, Eds. New York, NY: Springer New York, 2013, pp. 245–284. doi: 10.1007/978-1-4614-5395-6_8.
[24] S. Sargazi *et al.*, "CoNi alloy nanoparticles for cancer theranostics: synthesis, physical characterization, in vitro and in vivo studies," *Appl. Phys. A*, vol. 127, no. 10, p. 772, Sep. 2021, doi: 10.1007/s00339-021-04917-8.
[25] K. Fukuda, S. Fujieda, K. Shinoda, S. Suzuki, and B. Jeyadevan, "Low temperature synthesis of FePt alloy nanoparticles by polyol process," *J. Phys. Conf. Ser.*, vol. 352, p. 012020, Mar. 2012, doi: 10.1088/1742-6596/352/1/012020.
[26] S. Ansari *et al.*, "Magnetic Iron Oxide Nanoparticles: Synthesis, Characterization and Functionalization for Biomedical Applications in the Central Nervous System," *Materials*, vol. 12, no. 3, p. 465, Feb. 2019, doi: 10.3390/ma12030465.
[27] V. Dubey and V. Kain, "Synthesis of magnetite by coprecipitation and sintering and its characterization," *Mater. Manuf. Process.*, vol. 33, no. 8, pp. 835–839, Jun. 2018, doi: 10.1080/10426914.2017.1401720.
[28] S. Majidi, F. Zeinali Sehrig, S. M. Farkhani, M. Soleymani Goloujeh, and A. Akbarzadeh, "Current methods for synthesis of magnetic nanoparticles," *Artif. Cells Nanomedicine Biotechnol.*, vol. 44, no. 2, pp. 722–734, Feb. 2016, doi: 10.3109/21691401.2014.982802.

[29] J. K. Patra and K.-H. Baek, "Green Nanobiotechnology: Factors Affecting Synthesis and Characterization Techniques," *J. Nanomater.*, vol. 2014, pp. 1–12, 2014, doi: 10.1155/2014/417305.
[30] M. Mahdavi *et al.*, "Synthesis, Surface Modification and Characterisation of Biocompatible Magnetic Iron Oxide Nanoparticles for Biomedical Applications," *Molecules*, vol. 18, no. 7, Art. no. 7, Jul. 2013, doi: 10.3390/molecules18077533.
[31] J. I. Park and J. Cheon, "Synthesis of 'solid solution' and 'core-shell' type cobalt--platinum magnetic nanoparticles via transmetalation reactions," *J. Am. Chem. Soc.*, vol. 123, no. 24, pp. 5743–5746, Jun. 2001, doi: 10.1021/ja0156340.
[32] Y. Piao *et al.*, "Wrap–bake–peel process for nanostructural transformation from β-FeOOH nanorods to biocompatible iron oxide nanocapsules," *Nat. Mater.*, vol. 7, no. 3, pp. 242–247, Mar. 2008, doi: 10.1038/nmat2118.
[33] C. Liu *et al.*, "Reduction of Sintering during Annealing of FePt Nanoparticles Coated with Iron Oxide," *Chem. Mater.*, vol. 17, no. 3, pp. 620–625, Feb. 2005, doi: 10.1021/cm0403457.
[34] A.-H. Lu, E. L. Salabas, and F. Schüth, "Magnetic Nanoparticles: Synthesis, Protection, Functionalization, and Application," *Angew. Chem. Int. Ed.*, vol. 46, no. 8, pp. 1222–1244, Feb. 2007, doi: 10.1002/anie.200602866.
[35] M. Mikhaylova *et al.*, "Superparamagnetism of Magnetite Nanoparticles: Dependence on Surface Modification," *Langmuir*, vol. 20, no. 6, pp. 2472–2477, Mar. 2004, doi: 10.1021/la035648e.
[36] M. Green, "Organometallic based strategies for metal nanocrystal synthesis," *Chem. Commun.*, no. 24, p. 3002, 2005, doi: 10.1039/b501835h.
[37] T. Hyeon, "Chemical synthesis of magnetic nanoparticles," *Chem. Commun.*, no. 8, pp. 927–934, Apr. 2003, doi: 10.1039/b207789b.
[38] U. Jeong, X. Teng, Y. Wang, H. Yang, and Y. Xia, "Superparamagnetic Colloids: Controlled Synthesis and Niche Applications," *Adv. Mater.*, vol. 19, no. 1, pp. 33–60, Jan. 2007, doi: 10.1002/adma.200600674.
[39] S.-H. Hu, B.-J. Liao, C.-S. Chiang, P.-J. Chen, I.-W. Chen, and S.-Y. Chen, "Core-Shell Nanocapsules Stabilized by Single-Component Polymer and Nanoparticles for Magneto-Chemotherapy/Hyperthermia with Multiple Drugs," *Adv. Mater.*, vol. 24, no. 27, pp. 3627–3632, Jul. 2012, doi: 10.1002/adma.201201251.
[40] S. Ota, N. Yamazaki, A. Tomitaka, T. Yamada, and Y. Takemura, "Hyperthermia Using Antibody-Conjugated Magnetic Nanoparticles and Its Enhanced Effect with Cryptotanshinone," *Nanomaterials*, vol. 4, no. 2, pp. 319–330, Apr. 2014, doi: 10.3390/nano4020319.
[41] P. M. Jurek, K. Zabłocki, U. Waśko, M. Mazurek, J. Otlewski, and F. Jeleń, "Anti-FGFR1 aptamer-tagged superparamagnetic conjugates for anticancer hyperthermia therapy," *Int. J. Nanomedicine*, vol. Volume 12, pp. 2941–2950, Apr. 2017, doi: 10.2147/IJN.S125231.
[42] S. Kossatz *et al.*, "Efficient treatment of breast cancer xenografts with multifunctionalized iron oxide nanoparticles combining magnetic hyperthermia and anti-cancer drug delivery," *Breast Cancer Res.*, vol. 17, no. 1, p. 66, Dec. 2015, doi: 10.1186/s13058-015-0576-1.
[43] F.-C. Lin, C.-H. Hsu, and Y.-Y. Lin, "Nano-therapeutic cancer immunotherapy using hyperthermia-induced heat shock proteins: insights from mathematical modeling," *Int. J. Nanomedicine*, vol. Volume 13, pp. 3529–3539, Jun. 2018, doi: 10.2147/IJN.S166000.
[44] T. Kobayashi, K. Kakimi, E. Nakayama, and K. Jimbow, "Antitumor immunity by magnetic nanoparticle-mediated hyperthermia," *Nanomed.*, vol. 9, no. 11, pp. 1715–1726, Aug. 2014, doi: 10.2217/nnm.14.106.
[45] A. Ito, H. Honda, and T. Kobayashi, "Cancer immunotherapy based on intracellular hyperthermia using magnetite nanoparticles: a novel concept of 'heat-controlled necrosis' with heat shock protein expression," *Cancer Immunol. Immunother.*, vol. 55, no. 3, pp. 320–328, Mar. 2006, doi: 10.1007/s00262-005-0049-y.

[46] P. K. Srivastava, A. Menoret, S. Basu, R. J. Binder, and K. L. McQuade, "Heat Shock Proteins Come of Age: Primitive Functions Acquire New Roles in an Adaptive World," *Immunity*, vol. 8, no. 6, pp. 657–665, Jun. 1998, doi: 10.1016/S1074-7613(00)80570-1.

[47] M. Suto *et al.*, "Heat dissipation mechanism of magnetite nanoparticles in magnetic fluid hyperthermia," *J. Magn. Magn. Mater.*, vol. 321, no. 10, pp. 1493–1496, May 2009, doi: 10.1016/j.jmmm.2009.02.070.

[48] A. Hervault and N. T. K. Thanh, "Magnetic nanoparticle-based therapeutic agents for thermo-chemotherapy treatment of cancer," *Nanoscale*, vol. 6, no. 20, pp. 11553–11573, 2014, doi: 10.1039/C4NR03482A.

[49] L. Chen, C. Chen, P. Wang, and T. Song, "Mechanisms of Cellular Effects Directly Induced by Magnetic Nanoparticles under Magnetic Fields," *J. Nanomater.*, vol. 2017, pp. 1–13, 2017, doi: 10.1155/2017/1564634.

[50] H. Demirci, N. Slimani, M. Pawar, R. E. Kumon, P. Vaishnava, and C. G. Besirli, "Magnetic Hyperthermia in Y79 Retinoblastoma and ARPE-19 Retinal Epithelial Cells: Tumor Selective Apoptotic Activity of Iron Oxide Nanoparticle," *Transl. Vis. Sci. Technol.*, vol. 8, no. 5, p. 18, Sep. 2019, doi: 10.1167/tvst.8.5.18.

[51] R. A. Revia, "Magnetite nanoparticles for cancer diagnosis, treatment, and treatment monitoring: recent advances," *Mater. Today*, vol. 00, no. 00, p. 12, 2015.

[52] V. Revuri, K. J. Cho, and Y. Lee, "Photosensitizer conjugated iron oxide nanoparticles for simultaneous in vitro magneto-fluorescent imaging guided photodynamic therapy," p. 4, 2015.

[53] M. F. Casula, Y. Jun, D. J. Zaziski, E. M. Chan, A. Corrias, and A. P. Alivisatos, "The Concept of Delayed Nucleation in Nanocrystal Growth Demonstrated for the Case of Iron Oxide Nanodisks," p. 8.

[54] S. G. Kwon *et al.*, "Kinetics of Monodisperse Iron Oxide Nanocrystal Formation by 'Heating-Up' Process," p. 14.

[55] A. Akbarzadeh, M. Samiei, and S. Davaran, "Magnetic nanoparticles: preparation, physical properties, and applications in biomedicine," *Nanoscale Res. Lett.*, vol. 7, no. 1, p. 144, Dec. 2012, doi: 10.1186/1556-276X-7-144.

[56] Y. Mi, Z. Shao, J. Vang, O. Kaidar-Person, and A. Z. Wang, "Application of nanotechnology to cancer radiotherapy," *Cancer Nanotechnol.*, vol. 7, no. 1, p. 11, Dec. 2016, doi: 10.1186/s12645-016-0024-7.

[57] B. Chertok, A. E. David, and V. C. Yang, "Polyethyleneimine-modified iron oxide nanoparticles for brain tumor drug delivery using magnetic targeting and intra-carotid administration," *Biomaterials*, vol. 31, no. 24, pp. 6317–6324, Aug. 2010, doi: 10.1016/j.biomaterials.2010.04.043.

[58] B. Chertok, A. E. David, B. A. Moffat, and V. C. Yang, "Substantiating in vivo magnetic brain tumor targeting of cationic iron oxide nanocarriers via adsorptive surface masking," *Biomaterials*, vol. 30, no. 35, pp. 6780–6787, Dec. 2009, doi: 10.1016/j.biomaterials.2009.08.040.

[59] M. Mahmoudi, H. Hofmann, B. Rothen-Rutishauser, and A. Petri-Fink, "Assessing the In Vitro and In Vivo Toxicity of Superparamagnetic Iron Oxide Nanoparticles," *Chem. Rev.*, p. 16, 2012.

[60] N. Singh, G. J. S. Jenkins, R. Asadi, and S. H. Doak, "Potential toxicity of superparamagnetic iron oxide nanoparticles (SPION)," *Nano Rev.*, vol. 1, no. 1, p. 5358, Jan. 2010, doi: 10.3402/nano.v1i0.5358.

[61] E. Blanco, H. Shen, and M. Ferrari, "Principles of nanoparticle design for overcoming biological barriers to drug delivery," *Nat. Biotechnol.*, vol. 33, no. 9, pp. 941–951, Sep. 2015, doi: 10.1038/nbt.3330.

[62] T. K. Jain, M. K. Reddy, M. A. Morales, D. L. Leslie-Pelecky, and V. Labhasetwar, "Biodistribution, Clearance, and Biocompatibility of Iron Oxide Magnetic Nanoparticles in Rats," *Mol. Pharm.*, vol. 5, no. 2, pp. 316–327, Apr. 2008, doi: 10.1021/mp7001285.

[63] A. Kunzmann, B. Andersson, T. Thurnherr, H. Krug, A. Scheynius, and B. Fadeel, "Toxicology of engineered nanomaterials: Focus on biocompatibility, biodistribution and biodegradation,"

Biochim. Biophys. Acta BBA - Gen. Subj., vol. 1810, no. 3, pp. 361–373, Mar. 2011, doi: 10.1016/j.bbagen.2010.04.007.

[64] L. H. Reddy, J. L. Arias, J. Nicolas, and P. Couvreur, "Magnetic Nanoparticles: Design and Characterization, Toxicity and Biocompatibility, Pharmaceutical and Biomedical Applications," *Chem. Rev.*, vol. 112, no. 11, pp. 5818–5878, Nov. 2012, doi: 10.1021/cr300068p.

[65] G. Jarockyte *et al.*, "Accumulation and Toxicity of Superparamagnetic Iron Oxide Nanoparticles in Cells and Experimental Animals," *Int. J. Mol. Sci.*, vol. 17, no. 8, p. E1193, Aug. 2016, doi: 10.3390/ijms17081193.

[66] G. Liu, J. Gao, H. Ai, and X. Chen, "Applications and potential toxicity of magnetic iron oxide nanoparticles," *Small Weinh. Bergstr. Ger.*, vol. 9, no. 9–10, pp. 1533–1545, May 2013, doi: 10.1002/smll.201201531.

[67] C. C. Berry, S. Wells, S. Charles, G. Aitchison, and A. S. G. Curtis, "Cell response to dextran-derivatised iron oxide nanoparticles post internalisation," *Biomaterials*, vol. 25, no. 23, pp. 5405–5413, Oct. 2004, doi: 10.1016/j.biomaterials.2003.12.046.

[68] E. J. van den Bos *et al.*, "Improved efficacy of stem cell labeling for magnetic resonance imaging studies by the use of cationic liposomes," *Cell Transplant.*, vol. 12, no. 7, pp. 743–756, 2003, doi: 10.3727/000000003108747352.

[69] A. Stroh *et al.*, "Iron oxide particles for molecular magnetic resonance imaging cause transient oxidative stress in rat macrophages," *Free Radic. Biol. Med.*, vol. 36, no. 8, pp. 976–984, Apr. 2004, doi: 10.1016/j.freeradbiomed.2004.01.016.

[70] B. Díaz *et al.*, "Assessing methods for blood cell cytotoxic responses to inorganic nanoparticles and nanoparticle aggregates," *Small Weinh. Bergstr. Ger.*, vol. 4, no. 11, pp. 2025–2034, Nov. 2008, doi: 10.1002/smll.200800199.

[71] S. Schöttler, K. Landfester, and V. Mailänder, "Controlling the Stealth Effect of Nanocarriers through Understanding the Protein Corona," *Angew. Chem. Int. Ed Engl.*, vol. 55, no. 31, pp. 8806–8815, Jul. 2016, doi: 10.1002/anie.201602233.

[72] H. H. Gustafson, D. Holt-Casper, D. W. Grainger, and H. Ghandehari, "Nanoparticle Uptake: The Phagocyte Problem," *Nano Today*, vol. 10, no. 4, pp. 487–510, Aug. 2015, doi: 10.1016/j.nantod.2015.06.006.

[73] A. E. Nel *et al.*, "Understanding biophysicochemical interactions at the nano-bio interface," *Nat. Mater.*, vol. 8, no. 7, pp. 543–557, Jul. 2009, doi: 10.1038/nmat2442.

[74] M. A. Dobrovolskaia, P. Aggarwal, J. B. Hall, and S. E. McNeil, "Preclinical studies to understand nanoparticle interaction with the immune system and its potential effects on nanoparticle biodistribution," *Mol. Pharm.*, vol. 5, no. 4, pp. 487–495, Aug. 2008, doi: 10.1021/mp800032f.

[75] H. Amiri *et al.*, "Protein corona affects the relaxivity and MRI contrast efficiency of magnetic nanoparticles," *Nanoscale*, vol. 5, no. 18, pp. 8656–8665, Sep. 2013, doi: 10.1039/c3nr00345k.

[76] M. M. Yallapu *et al.*, "Implications of protein corona on physico-chemical and biological properties of magnetic nanoparticles," *Biomaterials*, vol. 46, pp. 1–12, Apr. 2015, doi: 10.1016/j.biomaterials.2014.12.045.

[77] M. Mahmoudi, I. Lynch, M. R. Ejtehadi, M. P. Monopoli, F. B. Bombelli, and S. Laurent, "Protein-nanoparticle interactions: opportunities and challenges," *Chem. Rev.*, vol. 111, no. 9, pp. 5610–5637, Sep. 2011, doi: 10.1021/cr100440g.

[78] T. Cedervall *et al.*, "Understanding the nanoparticle-protein corona using methods to quantify exchange rates and affinities of proteins for nanoparticles," *Proc. Natl. Acad. Sci. U. S. A.*, vol. 104, no. 7, pp. 2050–2055, Feb. 2007, doi: 10.1073/pnas.0608582104.

[79] M. K. Yu *et al.*, "Drug-loaded superparamagnetic iron oxide nanoparticles for combined cancer imaging and therapy in vivo," *Angew. Chem. Int. Ed Engl.*, vol. 47, no. 29, pp. 5362–5365, 2008, doi: 10.1002/anie.200800857.

[80] R. Tietze *et al.*, "Efficient drug-delivery using magnetic nanoparticles--biodistribution and therapeutic effects in tumour bearing rabbits," *Nanomedicine Nanotechnol. Biol. Med.*, vol. 9, no. 7, pp. 961–971, Oct. 2013, doi: 10.1016/j.nano.2013.05.001.

[81] J. W. Bulte *et al.*, "Magnetodendrimers allow endosomal magnetic labeling and in vivo tracking of stem cells," *Nat. Biotechnol.*, vol. 19, no. 12, pp. 1141–1147, Dec. 2001, doi: 10.1038/nbt1201-1141.

[82] U. O. Häfeli *et al.*, "Cell uptake and in vitro toxicity of magnetic nanoparticles suitable for drug delivery," *Mol. Pharm.*, vol. 6, no. 5, pp. 1417–1428, Oct. 2009, doi: 10.1021/mp900083m.

[83] I. Lynch, K. A. Dawson, and S. Linse, "Detecting cryptic epitopes created by nanoparticles," *Sci. STKE Signal Transduct. Knowl. Environ.*, vol. 2006, no. 327, p. pe14, Mar. 2006, doi: 10.1126/stke.3272006pe14.

[84] S. I. Jenkins *et al.*, "'Stealth' nanoparticles evade neural immune cells but also evade major brain cell populations: Implications for PEG-based neurotherapeutics," *J. Control. Release Off. J. Control. Release Soc.*, vol. 224, pp. 136–145, Feb. 2016, doi: 10.1016/j.jconrel.2016.01.013.

[85] A. Lassenberger, A. Scheberl, A. Stadlbauer, A. Stiglbauer, T. Helbich, and E. Reimhult, "Individually Stabilized, Superparamagnetic Nanoparticles with Controlled Shell and Size Leading to Exceptional Stealth Properties and High Relaxivities," *ACS Appl. Mater. Interfaces*, vol. 9, no. 4, pp. 3343–3353, Feb. 2017, doi: 10.1021/acsami.6b12932.

[86] M. Pernia Leal, S. Rivera-Fernández, J. M. Franco, D. Pozo, J. M. de la Fuente, and M. L. García-Martín, "Long-circulating PEGylated manganese ferrite nanoparticles for MRI-based molecular imaging," *Nanoscale*, vol. 7, no. 5, pp. 2050–2059, Feb. 2015, doi: 10.1039/c4nr05781c.

[87] M. Rahimi, V. Shafiei-Irannejad, K. D Safa, and R. Salehi, "Multi-branched ionic liquid-chitosan as a smart and biocompatible nano-vehicle for combination chemotherapy with stealth and targeted properties," *Carbohydr. Polym.*, vol. 196, pp. 299–312, Sep. 2018, doi: 10.1016/j.carbpol.2018.05.059.

[88] M. Pernia Leal, C. Caro, and M. L. García-Martín, "Shedding light on zwitterionic magnetic nanoparticles: limitations for in vivo applications," *Nanoscale*, vol. 9, no. 24, pp. 8176–8184, Jun. 2017, doi: 10.1039/c7nr01607g.

[89] K. Pombo García *et al.*, "Zwitterionic-coated 'stealth' nanoparticles for biomedical applications: recent advances in countering biomolecular corona formation and uptake by the mononuclear phagocyte system," *Small Weinh. Bergstr. Ger.*, vol. 10, no. 13, pp. 2516–2529, Jul. 2014, doi: 10.1002/smll.201303540.

[90] B. Gleich and J. Weizenecker, "Tomographic imaging using the nonlinear response of magnetic particles," *Nature*, vol. 435, no. 7046, pp. 1214–1217, Jun. 2005, doi: 10.1038/nature03808.

