Gels Horizons: From Science to Smart Materials

K. S. Joshy
Thomas Sabu
Vijay Kumar Thakur *Editors*

Magnetic Nanoparticles

A New Platform for Drug Delivery

Springer

Gels Horizons: From Science to Smart Materials

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Editors
K. S. Joshy
IIUCNN
Mahatma Gandhi University
Kottayam, Kerala, India

Thomas Sabu
IIUCNN
Mahatma Gandhi University
Kottayam, Kerala, India

Vijay Kumar Thakur
School of Aerospace, Transport and Manufacturing
Cranfield University
Bedford, UK

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Preface

Targeted delivery of anticancer drugs is regarded as one of the supports of cancer treatment as it could allocate for improved treatment competence and less adverse effects. A promising drug delivery advance is magnetic drug targeting which can be recognized if a drug delivery vehicle holds a strong magnetic moment. Here, in this book, we discuss the diverse types of magnetic nanomaterials which can be used as magnetic drug delivery vehicles, approaches to magnetic targeted delivery as well as promising strategies for the enhancement of the image-guided delivery and the therapeutic action. The evolution in the progress of magnetic nanoparticle-based therapies for different biomedical applications is described here in this book. Most appreciably, magnetic nanoparticles have been extensively applied in drug delivery and hyperthermia treatment for cancer. However, current applications of magnetic nanoparticles reveal their promise toward decreasing implant infection and increasing tissue growth. To build the most efficient magnetic nanoparticle systems for diverse biomedical applications, numerous new applications of magnetic nanoparticles in the medical arena as well as remaining confronts for such clinical use are discussed in this book.

The book is divided into seven chapters that cover the synthesis, characterization and property of magnetic nanoparticles and their advancement in biomedical fields. The book also deals with the significant applications of magnetic nanoparticles for the treatment of cancer.

Chapter 1 "Magnetic Nanoparticles and Its Biomedical Applications" by Jeena Varghese discusses the development of nanoscience and nanotechnology for the advancement in the research and technologies based on magnetic nanoparticles. The possibility of tailoring its physicochemical properties including biocompatibility for the application of magnetic nanoparticles as a promising candidate in pharmaceutical and biomedical fields was also discussed. The applications such as disease therapy—extensively chemotherapy, drug delivery, MRI and tissue engineering —make use of MNPs in a wider range.

Chapter 2 titled "Surface Chemistry and Properties of Magnetic Nanoparticles" prepared by Anshida Mayeen et al. explains the surface chemistry and diversified applications of magnetic nanoparticles. Surface chemistry of magnetic

nanoparticles possesses a huge role in controlling different physical and chemical properties of magnetic nanoparticles. These nanostructures were applicable in diversified fields such as ultrahigh density data storage, nanomedicine, magneto-electric memory devices, in biosensing, magnetic resonance imaging, hyperthermia, gene and drug delivery.

Chapter 3 entitled "Magnetic Nanoparticles for Image-Guided Drug Delivery" by Ruby Varghese et al. summarizes physiochemical properties and pharmacokinetics of magnetic iron oxide nanoparticle as well as an attempt to provide an overview of hierarchical advances describing theranostic system which includes approaches and strategies utilized by magnetic iron oxide nanoparticle-based nanoplatform as well as enhancement in the application of image-guided drug delivery technique.

Chapter 4 "Magnetic and Fluorescent Nanogels for Nanomedicine" prepared by Vineeth M. Vijayan et al. summarizes some of the important fundamental fields related to this topic and how nanogels intersect with other important areas specifically targeting healthcare applications.

Chapter 5 entitled "Magnetic Glyconanoparticles for Biomedical Applications" prepared by Prajitha V. et al. presents the glyconanotechnology and application of magnetic glyconanoparticles in various fields such as drug delivery, bio-imaging, lectin binding, materials for controlled cell culture, surface modifiers, artificial tissues and artificial organic substrates due to their hydrophilic character and the ability of compatibility with bio-molecules.

Chapter 6, prepared by Sandhya Gopalakrishnan, entitled "Magnetic Nanoparticles for Hyperthermia a New Revolution in Cancer Treatment," reviews the latest advances in the field of magnetic nanoparticles, describing the important types with examples and major applications.

Chapter 7 "Magnetic Nanoparticles for Cancer Treatment," prepared by Subin Balachandran, gives a brief outlook of different approaches that are available for recognizing and curing cancer with the help of incorporation of magnetic nanoparticles. We have also discussed about the recent multimodal theranostic approaches which effectively reflects the application of nanotechnology in cancer therapy.

Kottayam, India — K. S. Joshy
Kottayam, India — Thomas Sabu
Bedford, UK — Vijay Kumar Thakur

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Editors and Contributors

About the Editors

K. S. Joshy is a post-doctoral researcher at the International and Inter University Center for Nanoscience and Nanotechnology, Mahatma Gandhi University, Kerala, India. His research interests include synthesis and characterization of nanoparticles with application for drug delivery. He has authored 10 research articles in high-impact journals, 1 book chapter and has been a co-editor on 1 book.

Thomas Sabu is currently Professor and Pro-Vice Chancellor in Mahatma Gandhi University, Kerala, India, in addition to being the founder director of the International and Inter University Centre for Nanoscience and Nanotechnology. After his B.Tech. in polymer science and rubber technology from University of Cochin, he went on to do his Ph.D. from Indian Institute of Technology, Kharagpur. Prof. Thomas is the Chief Editor of Nano-Structures and Nano-Objects and has received many national and international awards, including Fellowship of the Royal Society of Chemistry, MRSI award, SESR award, the Dr. A. P. J. Abdul Kalam Award for Scientific Excellence, an honorary degree by Université de Lorraine, and multiple fellowships by prestigious societies and universities. Prof. Thomas' research has spanned many areas of nanocomposite and polymer science and engineering, and he has edited more than 70 books, holds 5 patents and has authored over 750 research publications.

Dr. Vijay Kumar Thakur is currently a faculty member in the School of Aerospace, Transport and Manufacturing at Cranfield University. Prior to this, Dr. Thakur worked as a Staff Scientist in the School of Mechanical and Materials Engineering at Washington State University, US. Some of his other prior significant appointments include being a Research Scientist in Temasek Laboratories at Nanyang Technological University, Singapore and a Visiting Research Fellow in the Department of Chemical and Materials Engineering at LHU–Taiwan. He did his post-doctoral study in Materials Science and Engineering at Iowa State University

and received Ph.D. in Polymer Chemistry (2009). He received his B.Sc. (Chemistry, Physics and Mathematics), B.Ed. and M.Sc. degree in Organic Chemistry from Himachal Pradesh University, Shimla, India. Dr. Thakur is an editorial board member of several SCI peer reviewed international journals as well as member of scientific bodies around the globe.

Contributors

Subin Balachandran Department of Zoology, Sacred Heart College, Kochi, Kerala, India

John P. Bradford Polymers & Healthcare Materials/Devices, Department of Material Science and Engineering, University of Alabama at Birmingham, Birmingham, AL, USA

Yogesh Bharat Dalvi Pushpagiri Institute of Medical Sciences and Research Centre, Tiruvalla, Kerala, India

Jesiya Susan George International and Inter University Centre for Nano Science and Nanotechnology, Mahatma Gandhi University, Kottayam, Kerala, India;
School of Chemical Sciences, Mahatma Gandhi University, Kottayam, Kerala, India

Sandhya Gopalakrishnan Department of Prosthodontics, Government Dental College, Kottayam, Kerala, India

K. P. Jibin International and Inter University Centre for Nano Science and Nanotechnology, Mahatma Gandhi University, Kottayam, Kerala, India;
School of Chemical Sciences, Mahatma Gandhi University, Kottayam, Kerala, India

Nandakumar Kalarikkal School of Pure and Applied Physics, Mahatma Gandhi University, Kottayam, Kerala, India;
International and Inter University Centre for Nanoscience and Nanotechnology, Mahatma Gandhi University, Kottayam, Kerala, India

Anshida Mayeen School of Pure and Applied Physics, Mahatma Gandhi University, Kottayam, Kerala, India;
Department of Physics, Thangal Kunju Musaliar College of Engineering, Kollam, India

V. Prajitha International and Inter University Centre for Nano Science and Nanotechnology, Mahatma Gandhi University, Kottayam, Kerala, India;
School of Chemical Sciences, Mahatma Gandhi University, Kottayam, Kerala, India

V. R. Remya International and Inter University Centre for Nano Science and Nanotechnology, Mahatma Gandhi University, Kottayam, Kerala, India

Anju K. Sajan International and Inter University Centre for Nanoscience and Nanotechnology, Mahatma Gandhi University, Kottayam, Kerala, India

Riju K. Thomas Bharata Mata College, Thrikkakara, Kochi, Kerala, India

Sabu Thomas International and Inter University Centre for Nano Science and Nanotechnology, Mahatma Gandhi University, Kottayam, Kerala, India;
School of Chemical Sciences, Mahatma Gandhi University, Kottayam, Kerala, India

Vinoy Thomas Center for Nanoscale Materials and Biointegration, University of Alabama at Birmingham, Birmingham, AL, USA;
Polymers & Healthcare Materials/Devices, Department of Material Science and Engineering, University of Alabama at Birmingham, Birmingham, AL, USA

Bernabe S. Tucker Polymers & Healthcare Materials/Devices, Department of Material Science and Engineering, University of Alabama at Birmingham, Birmingham, AL, USA

Kannan Vaidyanathan Department of Biochemistry and Head Molecular Biology, Amrita Institute of Medical Science and Research Center, Kochi, Kerala, India

Jeena Varghese School of Pure & Applied Physics, Mahatma Gandhi University, Kottayam, India

Ruby Varghese Pushpagiri Institute of Medical Sciences and Research Centre, Tiruvalla, Kerala, India

I. S. Vidyalakshmi St. Berchmans College, Changanassery, Kottayam, Kerala, India

Namitha Vijay Pushpagiri Institute of Medical Sciences and Research Centre, Tiruvalla, Kerala, India

Vineeth M. Vijayan Center for Nanoscale Materials and Biointegration, University of Alabama at Birmingham, Birmingham, AL, USA;
Polymers & Healthcare Materials/Devices, Department of Material Science and Engineering, University of Alabama at Birmingham, Birmingham, AL, USA

Chapter 1
Magnetic Nanoparticles and Its Biomedical Applications

Jeena Varghese, I. S. Vidyalakshmi, and Riju K. Thomas

1 Nanoscience, Nanotechnology and Nanoparticles

Nanotechnology offers a broad spectrum of applications in almost all fields of science. The daily lives of humans changed after the development of nanoscience. As an example, the replacement of bulky electronic devices to tiny ones made our lives easier and more advanced. Nanoscience and technology follow a symbiotic relationship with each other. The technologies like scanning tunneling and scanning force microscopy enhanced the development of nanoscience. They provide images and operate objects on surfaces with adequate precision even in ambient surroundings or in liquids [1].

The word "nano" means "*dwarf*." Nanotechnology deals with both single nano-objects and materials, and devices based on them, and with processes that occur in the nanometer range [1, 2]. An illustration of the nanometer scale in comparison with the known systems is shown in Fig. 1. Typically, nanoparticles have dimension between 1 and 100 nm and possess significant differences in properties from the corresponding bulk material. Nanoparticle's research is one of the highly demanding areas of scientific research owing to its potential applications in biomedical, optical and electronic fields. Nanoparticles act as a bridge between bulk and atomic or molecular structures. The physical properties of bulk materials are constant irrespective of its size; however, when it comes to the nano-scale, the picture is different. For example, the quantum confinement in semiconductor particles, surface plasmon resonance in metallic nanoparticles and superparamagnetism

J. Varghese
School of Pure & Applied Physics, Mahatma Gandhi University, Kottayam 686560, India

I. S. Vidyalakshmi
St. Berchmans College, Changanassery, Kottayam, Kerala 686101, India

R. K. Thomas (✉)
Bharata Mata College, Thrikkakara, Kochi, Kerala 682021, India

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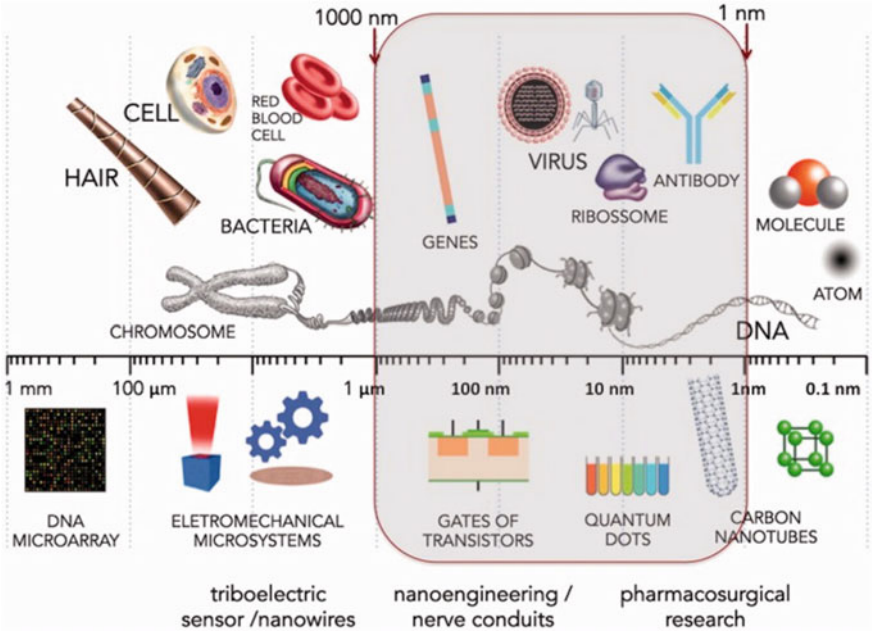

Fig. 1 Illustration of nano-scale range in comparison with the known systems. Adapted from Ref. [1]. Copyright obtained from Taylor & Francis 2017

in magnetic materials have size-dependent properties. When the size reduces to nano-scale, the properties of materials will also change. The percentage of atoms at the surface of a material becomes significant at this stage. One of the most size-dependent characteristic is their magnetic property. Hence, scientists prefer nanoparticles having sizes that are comparable with that of magnetic domains in the corresponding bulk materials [2].

The important physical characteristics of nanomaterials are prescribed by the nano-objects they contain. The two main classifications of nanomaterials are compact materials and nanodispersions. Nanostructured materials come under the category of compact materials. These materials are isotropic in the macroscopic composition, and they consist of contacting nanometer-sized units as repeating structural elements. In the second category, nanodispersions comprise a homogeneous dispersion medium like a vacuum, gas, liquid or solid and nano-sized inclusions diffused in this medium and secluded from each other. In these dispersions, the distance between the nanoparticles can be varied from fractions of a nanometer to tens of nanometers. The latter case deals with nanopowders whose grains are separated by thin layers of light atoms and thus prevent the agglomeration or cluster formation of these materials. The most interesting materials for magnetic investigations are the materials containing magnetic nanoparticles and isolated in non-magnetic matrices at the distances longer than their diameters.

2 Magnetic Nanoparticles

Nanomaterials having magnetic elements like iron, nickel, chromium, cobalt, manganese and their chemical compounds are commonly known as magnetic nanoparticles (MNPs). They are superparamagnetic in nature. These particles can be used both in their bare form or coated with a surface coating and functional groups chosen for specific uses. Among them, the most quested nanoparticles are the ferrite nanoparticles. These particles can be grown by clustering of a number of individual superparamagnetic nanoparticles. The cluster of these particles will form magnetic beads.

Under the action of an external magnetic field from an electromagnet or a permanent magnet, these magnetic nanoparticles can attach to a functional molecule, and thus, they allow the transportation to a targeted location. The surface coating helps to prevent the aggregation and reduces the interaction of the particles with the system environment. Their stability in the solution can be improved by using surfactants, silica, silicones or phosphoric acid derivatives. Overall, functionalized MNPs have been broadly used in quite a lot of medical applications, for instance, immunoassay, diagnostic testing, cell isolation and drug delivery [2–4].

2.1 Physical Properties of MNPs

The movement of particles having mass and electric charges such as electrons, protons, positive and negative ions in the material is responsible for magnetic effects. The magnetic dipole formed due to the spinning motion of the electrically charged particle is called a magneton. These magnetons can be seen as clusters in ferromagnetic materials. Some exchange forces make all these magnetons to align in the same direction in a ferromagnetic material, and this refers to the ferromagnetic domains. A ferromagnetic material can be distinguished from paramagnetic material due to these domains. A ferromagnetic material can be made into a single domain by decreasing its size below a critical value. The smallest free-energy state of ferromagnetic particles possesses uniform magnetization only when the size of the particle is smaller than a certain critical size, and all others will have a nonuniform magnetization. These are usually referred to as single-domain particles and multidomain particles, respectively. The hysteresis loop characterized by remanence and coercivity explains the nature of ferromagnetic materials in an applied magnetic field, in which the coercivity corresponds to the thickness of the curve. The coercivity is a size-dependent parameter. The size of a particle and coercivity has a Gaussian relationship. This means when the size of the particle decreases, coercivity increases to the maximum and then reduces to zero (Fig. 2).

Superparamagnetism will occur when the coercivity becomes zero. This will happen as the size of the single-domain particle further reduces below a critical diameter. Thermal effects are responsible for superparamagnetism. The thermal

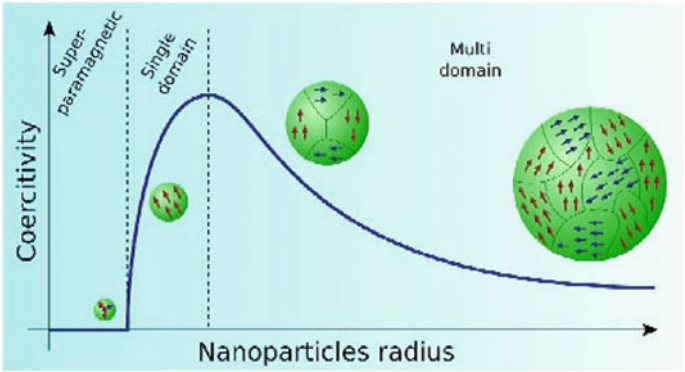

Fig. 2 Illustration of coercivity-size relation in MNPs. Adapted from Ref. [3]. Copyright obtained from Springer 2012

fluctuations in superparamagnetic particles are much stronger to spontaneously demagnetize a formerly saturated congregation. Thus, the coercivity of these particle will become zero and shows no hysteresis. Nanoparticles show magnetic behavior only in the presence of an external magnetic field, and all other times, they are in a non-magnetic state. This gives them an exceptional benefit of functioning in biological environments [3, 5, 6].

2.2 Magnetic Behavior of MNPs

There are five types of magnetism. The orbital motion of electrons in an atom produces atomic current loops, and they try to oppose the applied magnetic field. Most of the materials show this kind of repulsive behavior, and this is known as diamagnetism. Since the diamagnetism is very weak and other magnetic properties possessed by the material thus overpowers the effects of the current loops. Generally, the materials with filled electronic subshells whose magnetic moments are paired will show diamagnetic behavior. Since all the magnetic moments are paired, there will be zero magnetic moments. They also have a negative susceptibility ($\chi < 0$), and they are weakly repelled by a magnetic field. All these effects can be overcome only if there will be a net magnetic moment. Paramagnetic behavior can be seen in materials which possess uncoupled magnetic moments. Hence, here they have a small positive magnetic susceptibility ($\chi \sim 0$). Ferromagnetic materials have aligned atomic magnetic moments of equal magnitude. The crystalline structures of these ferromagnetic materials permit direct coupling interactions between the moments that cause an increase in the flux density. Since the magnetic moments are aligned in a ferromagnetic material, they show spontaneous magnetization in the absence of an external magnetic field (Fig. 3). Materials that retain permanent magnetization even after the removal of an external field are called hard

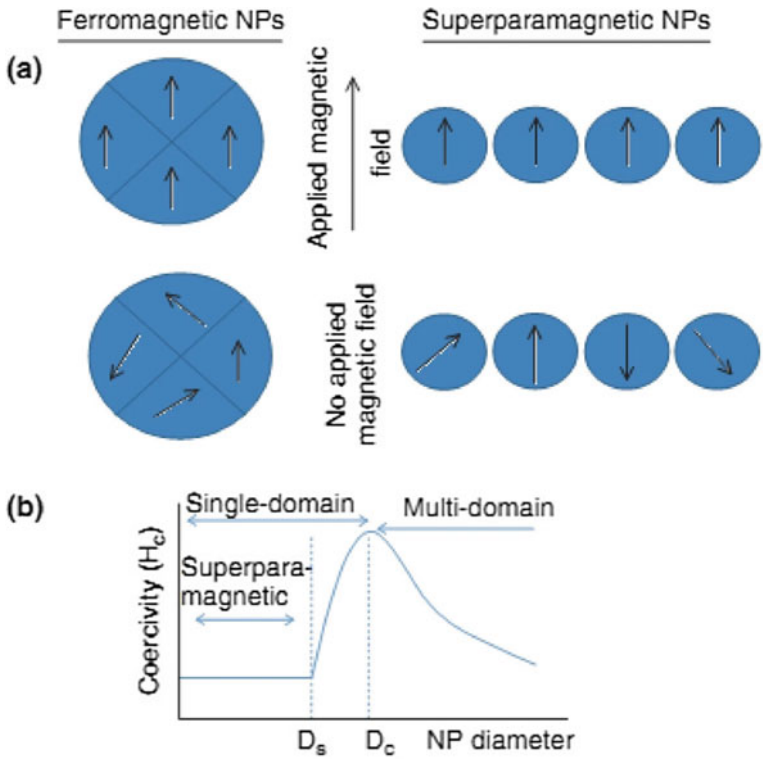

Fig. 3 **a** Ferromagnetic and superparamagnetic NPs; nature of magnetization under applied magnetic field. **b** Relationship of magnetic domain structures with particle diameter; D_s and D_c are the superparamagnetic and critical size thresholds. Adapted from ref. [3]. Copyright obtained from Springer 2012

magnets. Antiferromagnetism can be seen in materials having atomic magnetic moments of equal magnitude that are arranged in an antiparallel way. They also have a zero net magnetization. Above Neel temperature, the random fluctuation of equal and oppositely aligned atomic moments of materials exhibit paramagnetic behavior. As a consequence, their long-range order disappears. An ordered but nonparallel arrangement of atoms of some materials in a zero applied field below a certain characteristic temperature shows ferrimagnetic behavior. Commonly speaking, the antiparallel alignment of neighboring non-equivalent sublattices within a magnetic domain results in a substantial net magnetization [3, 5, 6].

2.2.1 Magnetocaloric Effect

The heating up of some magnetic materials in the presence of a magnetic field and cooling down after removing it is known as the magnetocaloric effect (MCE) [7].

The size-dependent superparamagnetic features of MNPs provide a capable substitute to conventional bulk materials. Since MNPs have a large surface area, they can provide a better heat exchange with the surrounding environment. We can control this heat exchange by carefully designing core–shell structures. This enables improved therapy technologies like hyperthermia.

2.3 Applications of MNPs

MNPs are potential candidates having a wide range of applications; some of them are given below.

2.3.1 High-Density Information Storage

The magnetic recording process is based on Faraday's electromagnetic induction principle. It consists of magnetic field generating "write head" with the help of current and thus changes the magnetization of closely spaced magnetic elements such as granules, particles or their groups in the magnetic medium. A part called "read head" generates the output signal by sensing the magnetization in the recording medium. This technology is now replaced by a modern magnetic recording system in which it stores digital data. Here, the write head receives the current in the form of digital data ('1' or '0'). The transition between the two possible magnetization states in the magnetic thin film media records the digital data. The data storage in usual hard disk media follows magnetization patterns in a film which contains tiny, feebly coupled magnetic grains, apiece of which behaves as a single-domain magnetic particle. Smaller the grain size, greater will be the data recording ability. The decrease in grain volume is followed by an increase in the magnetic anisotropy (K). But, for higher values of K, the recording head feels hard to produce sufficient field to write the data on the medium. This contradiction is called the superparamagnetic limit [2]. MNPs play a significant role in fast memory devices like magnetic random access memory (MRAM). They can replace the semiconductor memories used in modern computers—dynamic and static random access memory (DRAM and SRAM). The combination of a magnetic storage technology together with metal–oxide–semiconductor (MOS) devices result in fast and high-density data memory devices, and this is the technology behind the MRAM [8].

2.3.2 Environmental Applications of MNPs

Magnetic nanoparticles act as an agent for remediation of different types of contaminants in groundwater, soil and air. They are also used for exclusion of organic and inorganic pollutants. Removal of high concentration of organic compounds is

related to the elimination of dyes. The industrial products used in textile and paint factories contain dyes in high concentration. Hence, creating textile effluent with an adsorbent that contains MNPs can be a solution. Selective removal of hazardous metal ion toxins from complicated materials can be carried out by using MNPs carrying sorbents. Since the surface area of MNPs is very high as compared to the size of sorbents, we can easily remove metal ions from different sites. The important use of these MNPs sorbents is the recovery of metal ions from water wastes [3, 9, 10].

2.3.3 Analytical Applications of MNPs

Magnetic luminescent nanoparticles [MLNPs] have large surface area-to-volume ratio when compared to microbeads. This property makes them to have a good reaction homogeneity and faster reaction kinetics. Hence, making of magnetic fluorescent particles such as polystyrene with entrapped quantum dots [QDs] and iron oxide particles encrusted with dye-doped silica shells turns out to be easier. These are widely used in cellular imaging.

There is no need for centrifugation or filtration for the manipulation of MLNPs, which is due to their magnetic properties. The implementation of an internal calibration in the detected system is facilitated by their optical properties such as sharp emission, photostability and long lifetime [3, 11–13].

2.3.4 Catalytic Applications of MNPs

Recently, the limitation of heterogeneous catalysis is overcome by the catalysts incorporated with MNPs. The catalysts in a liquid-phase reaction can be easily recovered by magnetic separation rather than using filtration and centrifugation. Magnetically separable catalysts have high dispersion and reactivity with easy separation. Several transition metal-catalyzed reactions have evolved with catalytic sites grafted onto MNPs. Carbon–carbon cross-coupling reactions, polymerization, hydroformylation and hydrogenation are some examples [3, 14, 15].

3 Biomedical Applications of MNPs

Magnetic nanomaterials have proven its supreme potential in various domains like drug delivery, tissue engineering, hyperthermia and even in diagnostic systems like MRI. The magnetic properties combined with other characteristic properties enable it to be used in targeted systems with maximum functionality. Their applications are classified into two. For the external application of the human body, it is called as “in vitro” and for internal application of the human body, they are called “in vivo.” Some of the potential applications of MNPs [16] in biomedical field is illustrated in Fig. 4.

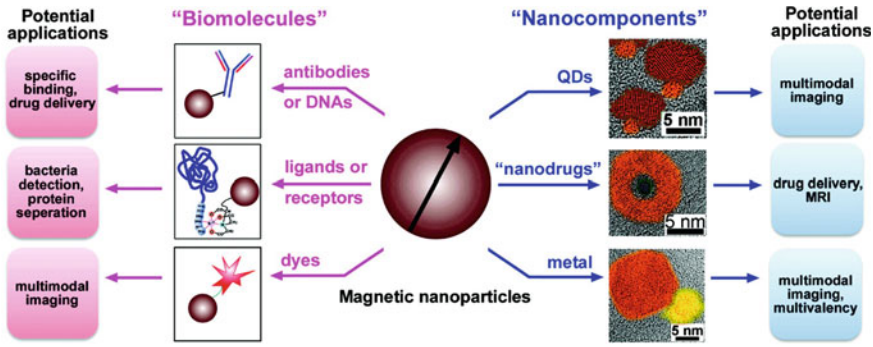

Fig. 4 Illustrating the fabrication scheme and the potential biomedical applications of MNPs. Adapted from Ref. [16]. Copyright obtained from American Chemical Society 2009

3.1 Drug Delivery

Drug delivery refers to the process of directing a pharmaceutical compound to the specific diseased site for achieving a therapeutic effect [17]. Conventional systems of drug delivery is often impaired by limited effectiveness due to poor specificity in reaching the targeted site, time of action, slow distribution, poor selectivity, reduced diffusion through biological barriers, etc., which leads to high incidence of adverse effects [18]. This could be potentially overwhelmed by the application of magnetic nanoparticles in targeted drug delivery [19]. Hence, the so-called smart magnetic material systems were developed and optimized to distribute the drugs within the body using the magnetic stimulus which is applied externally [20]. Widder, Senyei and their colleagues in the 1970s were the first to experiment the idea of using magnetic nanoparticles as a career in drug delivery [21]. The most desirable usage is in cancer therapy [22, 23] where nanoparticles were functionalized with certain polymeric (such as polymethyl methacrylate (PMMA) [24], PEG [25], etc.) or metallic coating loaded with drugs such as carboplatin, doxorubicin, paclitaxel, 5-fluorouracil, epirubicin [24–27] and injected so that it is directed to the tumor sites by an external magnetic field. And, this application requires the modification of size, surface chemistry, charge distribution and composition of nanoparticles making them viable for long time circulation.

There were many studies in the field of targeted drug delivery with magnetic guidance since the 1970s. Zimmermann and Pilwat made use of erythrocytes for the delivery of methotrexate, a cytotoxic drug. Lubbe et al. attempted the first animal study using MNPs, where small amounts of ferrofluid were used as vehicles to direct epirubicin locally in tumors [28, 29]. This did not produce any major abnormalities, and hence, magnetic fluid was termed safe and can be the best tool for cancer therapy. The research carried out in later years demonstrated that the

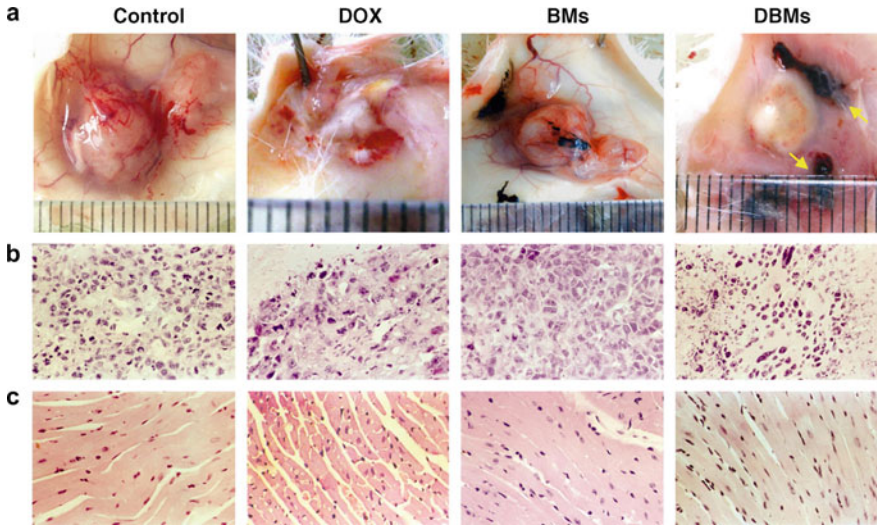

Fig. 5 **a** Images of the tumor regions **b** microphotograph of pathological sections (HE stains) from tumors **c** hearts. DBMs are indicated by the arrows. Adapted from Ref. [30]. Copyright Elsevier Ireland Ltd 2007

magnetic drug delivery by epirubicin was almost effective since it directed to tumors successfully [30]. Bacterial magnetosomes (BMs) were used as the drug carrier by Sun et al. which evidenced the antitumor effect of doxorubicin (DOX) loaded BMs (DBMs) in EMT-6 and HL60 cancer cell lines, thus suggesting the therapeutic potential of DBMs in targeted drug delivery against liver cancer [31] (Fig. 5). Polyak et al. investigated the mechanisms of cell delivery strategy by utilizing magnetic targeting of endothelial cells to the steel surfaces of intra-arterial stents by making cells magnetically responsive by loading with biodegradable superparamagnetic polymeric particles where the magnetic field gradients induce the exact direction of MNP-loaded cells to the stent wires [32]. Some studies demonstrate the successful targeting of MNP-loaded bovine aortic endothelial cells (BAECs) to stent wires.

Silica-coated Fe–C composite particles developed by high-energy ball milling and hydrogen reduction process are yet another candidate as an effective drug carrier demonstrated by Cao and his co-workers, where the composite particles possess properties like better drug absorption, desorption and powerful magnetic targeting. The in vivo experiment proved the prominent distribution of (TcO_4)-Tc-99m-adsorbed composite particles in the left hepatic lobe of pigs which are under study, which also proclaims the possibility of penetration through capillary wall around the tissue interstitium and hepatic cells by the help of external magnetic field [33].

Banerjee and Chen developed a multifunctional nano-carrier for drug targeting as well as sensing by coupling doxorubicin (DOX) to adipic dihydrazide-grafted

gum arabic-modified magnetic nanoparticles (ADH-GA-MNP) which are programmed to show the response to the variation of environmental stimuli (e.g., pH value). This DOX-ADH-GA-MNP stable at physiological pH (pH 7.4) can release DOX in an acidic environment (pH 5.0) [34]. Also, for the targeted delivery of hydrophobic drugs, magnetic nanoparticles modified by gum arabic and linking 2-hydroxypropyl-cyclodextrins (HCD) using hexamethylene diisocyanate (HMDI) were developed, and the resultant exhibited perfect capacity to direct all-trans-retinoic acid (ATRA), an anticancer agent [35].

Another significant application is in the drug delivery to brain parenchyma via the vascular endothelium of the blood–brain barrier using magnetic carriers. Stepp et al. designed an in vivo model to quantitatively determine the interaction between magnetically guided but freely blood circulating nanoparticles and the barrier illustrating the changes in cerebrovascular flow rate and volume [36]. Zhang and his co-workers utilized gum arabic-coated magnetic nanoparticles (GAMNP) to test the magnetic resonance imaging capability and drug delivery ability by the nanocarrier. The test results revealed the significant intake of GA-MNP in 9L glioma cells and its extra stable nature in aqueous media, making it a good candidate for MRI. Being an MRI-visible drug carrier, it can potentially be used both for tumor imaging and targeted intracellular drug delivery [37].

3.2 Magnetic Fluid Hyperthermia (MFH)

Hyperthermia refers to a medical therapy which exposes the human body with extreme temperature. This is utilized for the treatment of cancer. Numerous methods were developed for hyperthermia based on radio frequency, microwave and laser wavelengths, but magnetic nanoparticles based heating is of extreme importance as (i) the possibility of non-invasive method to increase the cell temperature to an optimum level (ii) can be easily visualized through MRI making diagnosis and therapeutic approaches combined (iii) the possible way of combining and functionalizing with other types of treatments such as chemotherapy or radiotherapy [38].

Thus, magnetic fluid hyperthermia (MFH) is a very promising method of cancer therapy which involves the injection of a magnetic fluid at an alternating magnetic field exposure (generally 250 kHz) and allows heat generation due to magnetic hysteresis loss [39]. The accumulated MNPs may reach a temperature which depends on their magnetic properties, the strength of the applied field, the frequency of oscillation and the cooling level of the blood flow in tumor region [40]. The heat generated may diffuse to the surrounding tissues due to the oscillation of magnetic moments inside the NPs [41]. Tumor cells seem to be more sensitive to heat due to its increased metabolism [42]. The heating mechanism is governed by Brown and Neel relaxation and can either be due to friction arising from total particle oscillations called Brown relaxation or Neel relaxation where rotation of magnetic moment with each field of oscillations generates heat [43]. And, these are highly

sensitive to the crystal size, the nature of the solvent (fluid viscosity) and particularly the magnetic properties of the material used [44, 45]. However, other nanomaterials with near-infrared (IR) absorption capabilities like gold nanoparticles [46] or carbon nano tubes [47] can also be made used for hyperthermia.

3.2.1 Clinical Evaluations

MFH has been widely investigated in animal and human models for cancer treatment since an increase of temperature in the range of 42–45 °C can irreversibly damage the tumor cells [39]. Also, it is convinced that a local heating for approximately 30 min is sufficient to destroy the tumor tissues [48], and if temperature exceeds 56 °C, thermoablations may occur (i.e., coagulation, necrosis and carbonization of the tissue) [49]. MNPs coated with stabilizers or by using encapsulated MNPs into delivery nanocarriers such as liposomes have been investigated extensively.

There were several reports concerning the magnetic nanoparticles usage for hyperthermia in animal models [50]. A systematic analysis of glioblastoma rat model was demonstrated for the invasive treatment of malignant brain tumors [51]. Two trials were done by intra-tumoral injection of carboxydextran-coated iron oxide (particle size 3 nm) and aminosilane-coated iron oxide (15 nm size) NPs in subsequent exposure to the alternative magnetic field. The former failed to achieve higher temperature than 39 °C and hence is poor antitumor responsive, whereas the later maintained high temperature and significant anticancer activity. This experiment could illustrate 4.5-fold increase in the chance of survival of so-treated rats. However, it significantly implements the importance of surface chemistry, i.e., the particle size and chemical nature of the functionalizing agents for the nanoparticle retention in the brain tissues. The year 2007 marked the breakthrough in this field when Maier-Hauff et al. experimented heating implanted magnetic nanoparticles in fourteen patients affected with recurrent glioblastoma multiforme. An aqueous solution of aminosilane-coated iron oxide nanoparticles with a core size of 15 nm was injected and exposed to 3.8–13.5 k/Am alternating magnetic field at 100 kHz. The MRI scans made could locate the tumor sites exactly. The CT scans and reproducible temperature measurements showed that all patients tolerated the nanoparticles without much complication and were stable for weeks [52]. Later, this method was combined with an external radiation dose which was reported to be safe and lead to longer tumor recurrence compared to conventional methods (Fig. 6) [53]. The same group also tried hyperthermic nanoparticles to treat prostate cancer.

A study on the intra-tumoral injection of MCLs (e.g., Fe_3O_4-encapsulated lipid mixture) into MM46 mammary tumor-bearing mice revealed an increase of temperature up to 45 °C at the surface of the tumor up on alternative magnetic field exposure for 30 min which resulted in tumor regression [54]. Interestingly, a repeated hyperthermia treatment developed antitumor immunity in these rats by heat shock proteins (HSPs) such as HSP70 or HSP72, which helps in immune cascade reactions [55]. Later on, HSP-70-mediated antitumor study was done in T-9

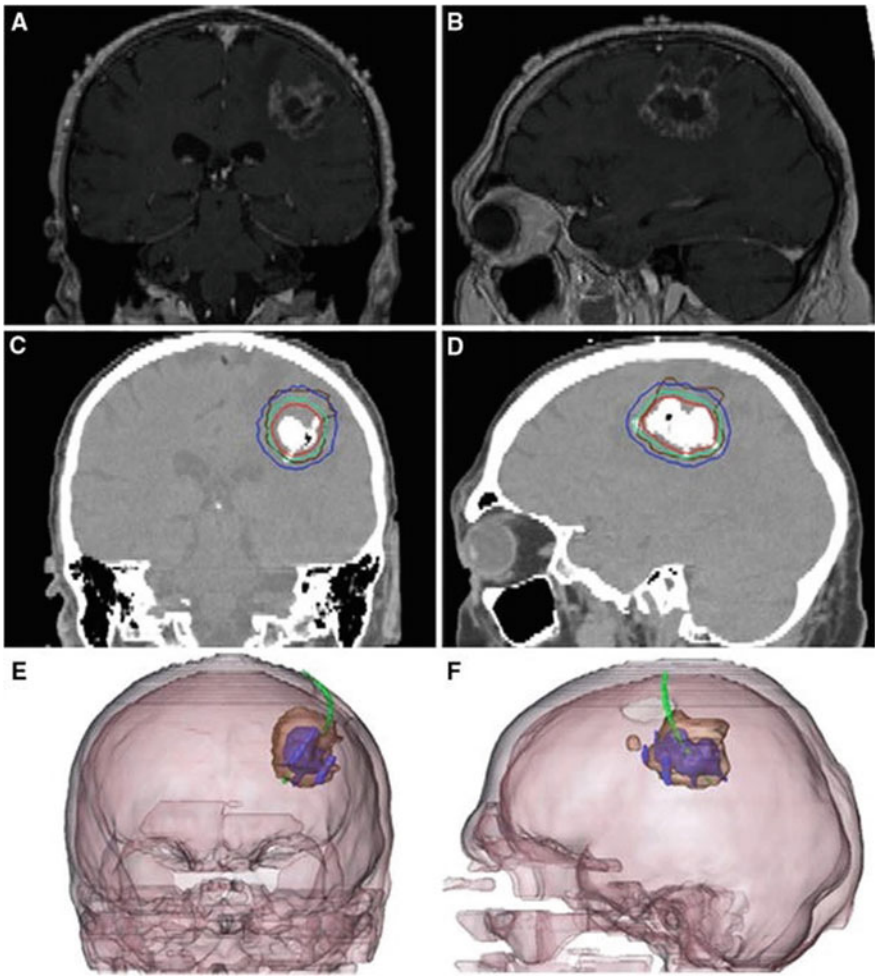

Fig. 6 **a**, **b** Pre-treatment MRI of the brain with glioblastoma. **c**, **d** CT scans after the injection of MNPs to the targeted site. The isothermal lines (blue and green) mark the specific temperature used for the treatment. **e**, **f** 3D model of the brain with tumor site (brown), MNPs fluid (blue) and thermometry catheter (green). Adapted from Ref. [53]. Copyright obtained from Springer Nature 2010

rat glioma model, which was successful in the tumor regression [56]. Another investigation on the therapeutic effect of MFH on an experimental human model of hepatocellular carcinoma xenograft significantly induced tumor proliferation and enhanced apoptosis [57].

Combining hyperthermia and chemotherapy is an efficient concept; for instance, iron oxide core covered with a thermo-sensitive polymer poly(*N*-iso-propylacrylamide) (PNIPAAm) was injected and was successful in demonstrating

temperature-triggered drug release [58]. The temperature increase due to applied magnetic field collapses the PNIPAAm and helps release the encapsulated drug [59].

Even though MFH is a promising method, it still needs improvements in (i) selective heat induction in affected region (ii) homogeneous distribution of temperature and (iii) reduction in invasiveness of the technique. This can be achieved by utilizing nanoparticles decorated with specific tumor cell targeting ligands such as MSb's [61], FA [62] or HER2 receptors [63] which can specifically bind to tumor cells enhancing the intracellular concentrations of MNPs. As an example, the antitumor drug tamoxifen (TMX) was loaded with SPIONs (particle size 12 nm) surface coated by β-cyclodextrin (CD) polymer and decorated by FA when subjected to alternating magnetic field resulted in temperature-triggered drug release (Fig. 7) [60].

3.3 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is a non-invasive imaging module depended on the relaxation properties of proton nuclei in water and lipids, capable of providing anatomical images in high-resolution. It is widely used as a tool for imaging pathological and physiological changes of living tissues in the body. Over computer tomography, it offers some advantages: (i) employs non-ionizing radio frequency (RF) signals for imaging and is compatible for non-calcified tissues in the body, (ii) wide range of detection depending on various scanning parameters, (iii) can create cross-sectional view in any images besides oblique planes, (iv) superior in tumor detection, (v) provides multiple examination facility in short period of time, (vi) multiple contrast systems like T_1-weighted, T_2-weighted and T_2^*-weighted MR images. T_1 relaxation referred as spin-lattice or longitudinal relaxation is a time constant of nuclear spins returning to equilibrium which is characterized by the return of the net magnetization to its ground state from a high energy state of maximum length along the direction of the main magnetic field. It is usually around 1 s for tissue. T_2 relaxation named as spin–spin or transverse relaxation is a time constant of signal decay occurs with the energy exchange between spins in the high and low energy state but not releasing energy to the surroundings. T_2 is around 100 ms for tissues. T_2^* is the time for the decay of transverse magnetization to decay to 37% of its original magnitude, produced under an inhomogeneous magnetic field [64]. Recently, iron oxide NPs (IONPs) was explored as efficient contrast agents for MRI [65].

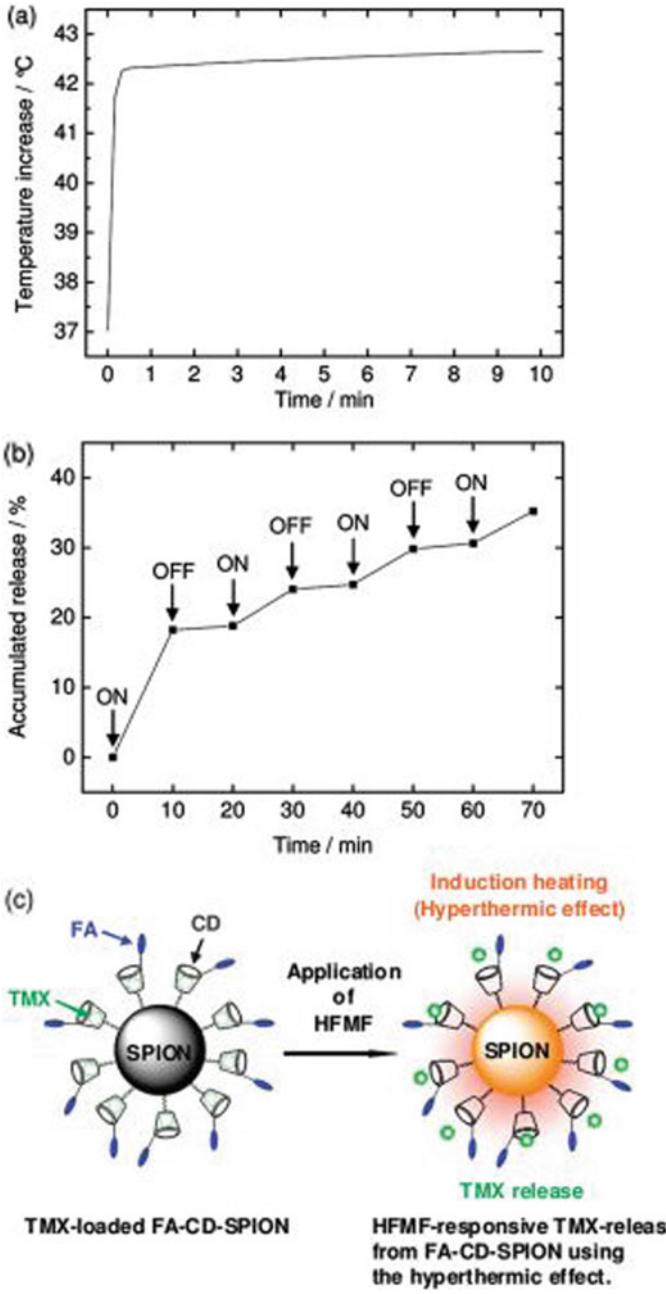

Fig. 7 **a** Illustration on temperature increase of the aqueous solution of TMX-loaded FA- and CD-decorated SPIONs under high magnetic field (frequency 230 kHz) **b** controlled release of TMX from FA-CD-SPIONs under magnetic response **c** schematic illustration of TMX release from FA-CD-SPIONs. Adapted from ref. [60]. Copyright American Chemical Society 2010

3.3.1 T1-Contrast Agents for MRI

Young et al. were the first to introduce Gd components based T_1 contrast agents which show functions like (i) components having a hydrophobic core with polypropylenimine diaminobutane (DAB) dendrimer can easily accumulate in liver, and hence, as liver contrast agents (ii) hydrophilic contrast agents can make lymphatic imaging. Also, the contrast agents based on gadolinium components targeted to antibodies [66], receptors [67], DNA [68] or functional peptides [69] can act as tumor-specifying agents with both diagnostic and therapeutic functions [70]. The Gd-based agents have applications in imaging functional anatomy of tumor blood vessels, e.g., in micro-MR angiography of normal and intra-tumoral vessels [71] and imaging internal organs like liver [72], spleen [73], lungs, kidney [74], brain [75] and lymphatic nodes system [76]. Luminescent nanoparticles of Gd_2O_3 covalently functionalized with polysiloxane which contain carboxylated PEG and organic fluorophores showed an enhancement of the positive contrast of MRI over the generally used contrast agents (Fig. 8). They are assumed to be better candidates in diagnostic and neutron capture therapy [77].

3.3.2 T_2/T_2^*-Contrast Agents for MRI

Ohgushi et al. developed T_2/T_2^* contrast agents for the first time based on superparamagnetic particles for MRI [78]. In the 1990s, Weissleder and co-workers

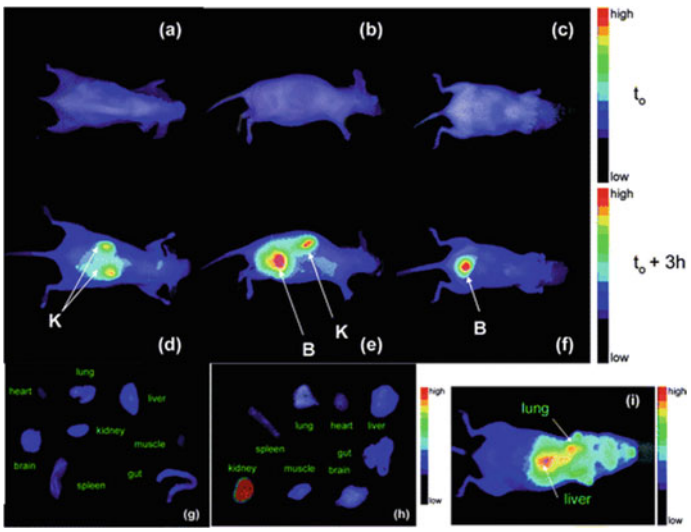

Fig. 8 Fluorescence imaging of a mouse **a**, **b**, **c** before and **d**, **e**, **f** 3 h after the injection of GadoSiPEG2C (K: kidneys and B: bladder). Adapted from Ref. [77]. Copyright obtained from American Chemical Society 2007

introduced ultra-small superparamagnetic iron oxide nanoparticles (USPIOs) for T_2/T_2^* contrast agents, which have core size of 4–6 nm. These USPIOs can produce strong transverse and longitudinal relaxation compared to Gd-based contrast agents [79]. And, these have wide applications in imaging of small molecules [80], targeted receptors [81], magnetically labeled cells [82], cell migration, atherosclerotic plaque, cell inflammation [83], tissue inflammation, reticuloendothelial systems (RES) [84] including liver, spleen, pancreatic islets, lung and lymph nodes. Dai et al. came up with FeCo/C core–single graphitic shell nanoparticles that showed ultrahigh saturation magnetization and r_1/r_2 relaxivities [85]. A preliminary investigation revealed long-term durable positive contrast enhancement for vascular MRI in a rabbit model. These core–shell structures can actually act as a dual-purpose agent for integrated diagnosis and therapeutic applications. Cheon group developed spinel ferrite nanoparticles conjugating with antibodies which can show an enhancement in T_2 signal for the cancer detection over commonly used probes [86]. Thus, the highly efficient magnetic nanoparticle systems can be used in the real-time imaging of biological samples, cell trafficking, cancer metastasis, cellular signaling and tumor diagnostics [87].

3.4 Cell Labeling and Imaging

Recently, cellular MRI has taken much attention that aids to visualize and track cells in biological systems. Iron oxide nanoparticles have gained much regards for in vivo imaging of cells transplanted into the body [88]. Various challenges include the (i) need of achieving high labeling of the cells which is primarily depended on the extent of absorption of IONPs by the cells, (ii) ensuring cell integrity and viability after labeling. Generally, the nanoparticle uptake by a cell is linearly dependent on the particle size. As an example, incubation of human monocytes with SPIONs (Endorem) showed 50 pg/cell iron concentration [89], whereas certain other cell types like murine hepatocytes, murine fibroblasts or mesenchymal stem cells when incubated with bigger particles (particle size 5.8 μm) achieved $\sim$100 pg/cell iron concentration [90]. Various approaches have been attempted to increase the labeling efficiency such as functionalizing with cell internalizing antibodies [91] or translocating agents, like HIV-1 Tat peptide [92], albumin induced transport [93] and the use of transfection agents. An example is the murine antirat transferrin mAb (mAb OX-26) coated at the surface of small-sized SPIONs produced excellent labeling of rat oligodendrocyte progenitor cell lines (CG-4) [91].

Transfection agents like lipofectamine, poly(L-lysine), poly(L-arginine), poly(L-ornithine), SuperFect (heat-activated dendrimer), protamine sulfate, etc., can be combined with IONps for enhanced labeling of cells [94]. But, there were certain limitations with this technique: (i) mixing of positively charged transfection agents with the negatively charged IONPs results in the loss of nanoparticle surface charge

which ultimately results in precipitation. (ii) cytotoxicity due to cell membrane perturbation (iii) nanoparticle adsorption on the cell surface [95]. Magnetic electroporation using IONPs is considerably important in preserving the cell integrity and successful labeling [96].

3.4.1 Imaging Transplanted Stem Cells

Stem cell transplantation is yet another important medical process in the context of regenerative medicine implemented for the treatment of heart failure, ventricular dysfunction, vascular injury, etc. It is done by vascular injection and subsequent MRI confirmation of its proper direction to the targeted sites [97]. For instance, the intravenous injection of ferumoxide-labeled human hematopoietic progenitor stem cells into athymic mice evidenced the distribution of labeled cells into liver, spleen and bone marrow which is indicated by a corresponding reduction of the MR signal intensity in these tissues. Surprisingly, injecting the SPION-labeled cells showed strong signal intensity drop suggesting a preferential homing of the labeled cells in the bone marrow. Yet another study in human embryonic stem (HES) cells labeled with dextran-coated IONPs revealed well-defined hypointense regions at the site of injection [98]. This approach is successful in monitoring and labeling the HES cell-based regenerative medicine. In a similar approach, human neural precursor cells labeled with IONPs and injected to mouse brain can be successfully tracked up to one month [99].

3.5 Tissue Engineering

Tissue engineering is an interdisciplinary science which integrates the principle of engineering, cell biology, biochemistry and medicine aiming the modification or reconstruction of cells or functional tissues. Biocompatible scaffolds in two or three dimensions are needed for the growth of cells leading to its further differentiation, proliferation and tissue formation. The cells here are cultured in vitro completely isolated from a tissue biopsy and seeded in the 3D scaffold. In this regard, achieving the efficient cell seeding and effective cell–cell interactions remains as a challenge. Magnetic force-based tissue engineering (Mag-TE) utilizes magnetic nano-devices (e.g., MCLs, magnetic gelatin NPs, MNP-loaded hydroxyapatite and collagen) for providing magneto response to the cells. MCLs were used to enhance the adhesion of human aortic endothelial cells (HAECs) on to a rat hepatocyte layer by the application of magnetic field for about 24 h. It seems connected even after the removal of the magnetic field [100]. The obtained heterotypic construct could secret albumin, whereas the one without modification failed in this functionality. Thus, multilayered tissue constructs could be developed which is depended on the concentration of magnetic particles in the cells and also the intensity of magnetic field applied.

Scaffold-based tissue engineering is so crucial since the scaffolds need to be non-toxic and bio-compatible which can be developed by various materials like polymers, agarose, etc. [101]. A challenging part is to achieve efficient packing of cells with high cell number at the interior of the scaffold. This can be achieved by (i) MCLs-loaded cells [102] or chitosan-coated MNPs [103] (ii) hydrating scaffold with cell suspension (iii) application of magnetic field. Here, cell seeding can be properly achieved in porous scaffolds with the application of external magnetic fields, and the field intensity has a high influence on the depth of cell seeding in the scaffolds.

Such a protocol has resulted in the cell seeding into the deeper sites of the three-dimensional porous scaffolds, while the absence of a magnetic field did not result in efficient cell germ. The magnetic field intensity has been found to have a positive influence on the depth of the cell seeding into the scaffold.

3.6 Magnetic Bio-Separation

Magnetic bio-separation refers to the separation of bio-components attached to the nanoparticle surface with magnetic susceptibility extracted by means of external magnetic field. Usually, superparamagnetic nanoparticles were used for the separation process, since they are easily magnetized in external magnetic field. The process involves making bio-entities conjugated with superparamagnetic nanomaterials and the separation of the labeled entities from the solutions using magnetic separator. The nanoparticles thus used should exhibit better dispersibility in the media, the capacity to distinguish and to interact with the target cells and ability to be accumulated under the influence of magnetic field. Various applications involve the separation and purification of cells, bacteria, proteins and nucleic acids (DNA and RNAs) [104].

3.6.1 Cell/Bacterial Separation

Cell separation using magnetic materials is a highly applicable domain which helps for the identification of the separated cells using MRI and its further processing. The magnetic nanoparticles so used should have good dispersibility in the media and the capability to track and interact with the targeted cells and the ability to accumulate in the magnetic field. The cell/bacterial separation has applications in clinical diagnosis, bioengineering and food engineering [105]. There are two ways in which cell/bacteria can be separated using external magnetic field: normal-phase separation where the targeted cells are being segregated from the mixed solutions and negative-phase separation which utilizes magnetic field for separating out the unnecessary cells from the solution, thereby allowing the accumulation of targeted cells alone.

There was much research in this area. Corato et al. used magnetic fluorescent colloidal nanobeads for bio-separation and sensing by incorporating fluorescent oligothiophene molecules to an amphiphilic polymer which covers the iron oxide nanoparticles [106]. Maeda and co-workers prepared a nanocomposite material with nanosized bacterial magnetic particles (BacMPs) and semiconductor quantum dots which are used for the targeting and identification of cancer cells [107]. Labeling of lung cancer cells was done by using nanocomposites conjugated with biotin carboxyl carrier protein (BCCP). There were many studies focusing on cell separation and cancer cell identification by utilizing magnetic nanobeads. A critical move toward the understanding and therapeutic targeting of cancerous cells is made by Suva et al. who utilized magnetic nanobeads for the identification of cancer stem cells in Ewing's Sarcoma family tumors (ESFT) [108]. Takahashi et al. attempted the separation of immune cells from the blood by using bacterial magnetic particles and also segregated melanoma-specific cytotoxic T lymphocytes using the same type of particles functionalized with MHC/peptide complex [109]. Pang and co-workers developed a scheme for the mapping of cell surface glycol conjugates and the separation of targeted cells using quantum dots and magnetic nanoparticles, based on the studies on magnetic glycol nanoparticles from Boubbou et al. (Figure 9) [110]. Ligand functionalized iron oxide nanoparticles (IONPs) also were used for the separation of apoptotic cells. Surface-enhanced Raman spectroscopy (SERS) allows pathogen-specific probes to be connected with IONPS and to detect the targeted pathogens [111]. A similar approach has been made for the separation of viruses: MNPs coupled with virus-specific globulin proteins were used for the separation of hepatitis B viral (HBV) and hepatitis C viral (HCV) particles from sera [112].

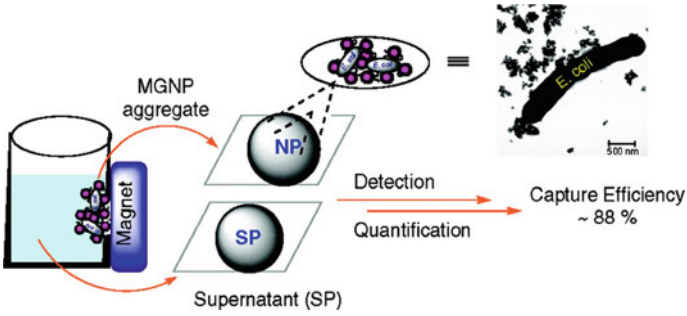

Fig. 9 Illustration of magnetic glycol nanoparticle (MGNP)-based system for the detection and separation of *E. coli*. Adapted from Ref. [110]. Copyright obtained from American Chemical Society 2007

Magnetic-Relaxation Switches

Magnetic-relaxation switches allow the sensing of molecular interactions like DNA–DNA, protein–protein, protein–small molecules and enzyme reactions even in turbid samples with the help of IONPs. The clustering of magnetic nanoprobes from independent particles to large assemblies allows spin–spin relaxation (T_2) which makes it efficient for detection by magnetic resonance relaxometry [113]. Here, the IONPs are usually combined with an oligonucleotide sequence or a protein which can identify the complementary sequence, binding allows reversible clustering and shortening of T_2 relaxation time [114]. This technique is also practically demonstrated for the detection of viruses such as adenovirus-5, herpes simplex virus-1 and bacteria such as *Mycobacterium avium* spp. paratuberculosis and *Staphylococcus aureus*, etc., in complex media like blood and milk [115].

3.6.2 Separation of Biochemicals

Isolating biochemicals from biological samples like serum, cell lysates, etc., can also be performed using MNPs. For instance, niobium oxide-coated MNPs can be used for the separation of phosphopeptides from peptides mixtures; where niobium oxide offers strong interactions with phosphonates making the selective enrichment of phosphopeptides from the complex media [116]. In a similar way, IONPs coupled with metal oxides like tantalum oxide, titanium dioxide, etc., can be used for the separation of phosphopeptide from tryptic digest samples. IONPs conjugated with double-stranded RNA (dsRNA) polyinosinic/polycytidylic acid can recognize (2-5) A synthetase of the freshwater sponge, followed by the isolation of NP-bound protein by the treatment with urea [117] (Fig. 10).

PS NPs surface conjugated with sulfonic cation exchanger groups and combined with IONPs in polyvinyl butyral has also been used for the isolation of proteins; the composite NPs (size $\sim$250 nm) get embedded in the PVB matrix could absorb the lysozyme before magnetic separation [118]. Yet, another example is the use of iminodiacetate-functionalized SiO_2-coated IONPs for protein purification where the Ni^{2+} surface charge on the NP surface makes it able to attach to the histidine-tagged proteins [119].

3.6.3 Enzyme/Protein Immobilization

Magnetic particles are gaining much interest as solid support for proteins and enzymes since it can offer easy recovery from complex biological mixtures. MNPs in the presence of carbodiimide and amphoteric hydroxyl groups can facilitate the immobilization of enzymes/proteins [120]. Some of the examples of enzymes are: Candida rugosa lipase, horseradish peroxidase, trypsin, α-chymotrypsin and porcine pancreas lipase [121]. Chitosan-coated IONPs surface coupled with enzymes such as adenosylhomocysteine nucleosidase (Pfs) and S-ribosylhomocysteinase (LuxS)

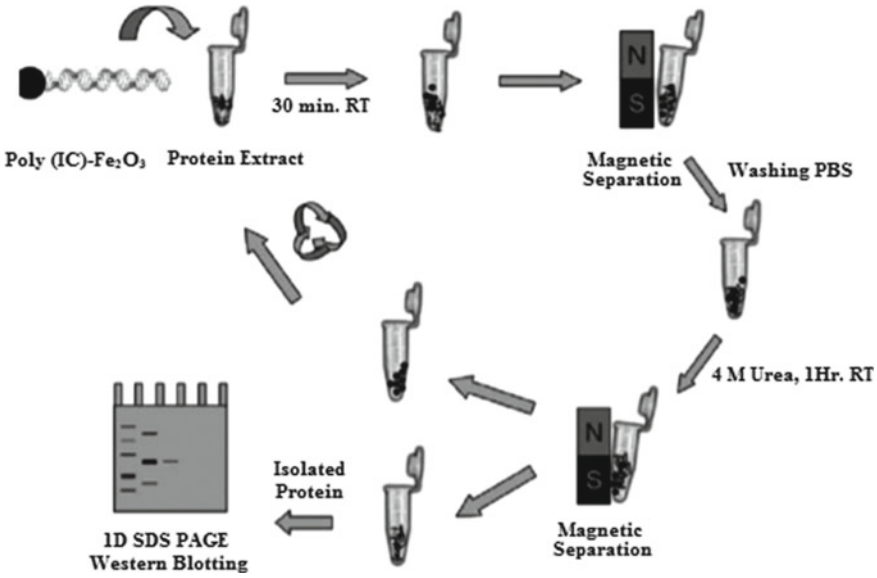

Fig. 10 Scheme of isolating (2-5). A synthetase from sponge extract using dsRNA poly(I:C) functionalized γ-Fe_2O_3 NPs. Adapted from ref [117]. Copyright 2007 RSC Publishing

combined in *Escherichia coli* bacterial suspension can facilitate the adhesion of NP on cell surface due to its positive electrical charge. A signaling molecule named as autoinducer-2 (AI-2) is formed on the bacterial surface by the reaction of Pfs and LuxS in the NP bound cells to an enzymatic substrate called S-adenosylhomocysteine (SAH). This penetrates the bacterial cell to alter the β-galactosidase expression, which have further application in manipulating the gene expressions (quorum sensing) so as to produce change in biofilm formation, pathogenicity and antibiotic resistance [122] (Fig. 11). Also, this has additional benefits in the development of next-generation antimicrobials [123].

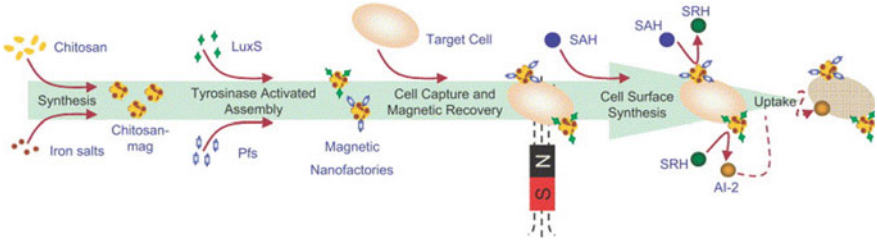

Fig. 11 Illustration of the synthesis of quorum signaling molecule autoinducer-2 (AI-2) development of magnetic nano-factories by tyrosinase activated assembly of Pfs and LuxS into chitosan-IONPs, capture of target cells, incorporation of SAH producing AI-2 and further cellular response. Adapted from Ref. [122]. Copyright obtained from Elsevier 2007

3.6.4 Bioanalysis and Immunoassays

Ligand-decorated IONPs have applications in bio-analysis and immunoassays due to its magnetic susceptibility and large surface area. In diagnostics, SPIONS can aid the immobilization of biomarkers for isolating and detecting proteins, enzymes and DNA [121]. In some reports, "nanotechnology-based bio-barcode-amplification method" has become superior over ELISA assay in the detection of HIV-1 p24 Gag protein [124]. This depends on MNPs (size $\sim$1000 nm) functionalized with antibodies and gold NPs (size $\sim$15 nm) doped with MAbs and barcode oligonucleotides that has sandwiching structure. The resultant sandwiched barcode DNA can be magnetically separated and treated under real-time polymerase chain reaction (PCR) and chip-based scanometric methods. And, this can produce the easy detection and isolation of HIV-1 antigens in a mixture of HIV-1 subtypes, where the sensitivity of detection is reported as 0.1 pg/mL.

Recently, a sandwich assay for DNA detection with two oligonucleotide sequences conjugated on gold NPs has been reported, one with complementary sequence to target DNA and the other with mismatched sequence known as barcode DNA [125]. This NP type together with IONPs conjugated to complementary sequence of remaining end of target DNA was hybridized with target DNA to form a sandwich complex. A quantization of absorbed fluorescence can be generated by fluorescent (Cy3-labeled and Cy5-labeled) DNA probes. In this analysis, the limit of detection is known to be 1 pM, which indicates the excellent sensitivity of this method (Fig. 12).

Surface-enhanced resonance Raman spectroscopy (SERRS)-based detection of P38 mitogen-activated protein kinase using microbead sandwich assay reports a detection limit of 9.5×10^{-12} mol/dm^3 and sensitivity even to low concentrations up to 6 ng/mL [126]. There were many studies on the sensitive detection of proteins using MNP-based immunoassays. IONPs coupled with parathyroid hormone antibody were used for the detection of parathyroid hormone which uses magneto-resistive sensor chips for detection. This is known to be an effective detection scheme for proteins in the picomolar concentration range [127].

3.6.5 Elimination of Metallic Impurities

MNPs can also be used in the elimination of heavy metal contaminants based on magnetic field separation which offers fast, cost-effective and easy removal of substances from mixtures [121]. As an example, γ-Fe_2O_3 NPs functionalized with poly(L-cysteine) for binding to soft metal acids and Fe_3O_4 NPs surface coated with poly(acrylic acid) which binds to cations can be heavy metal chelators [128]. Surface functionalization of IONPs with DMSA can be an excellent absorbent for toxic metals such as Hg, Ag, Pb, Cd and Ti, and this can be easily isolated by magnetic field separation [129].

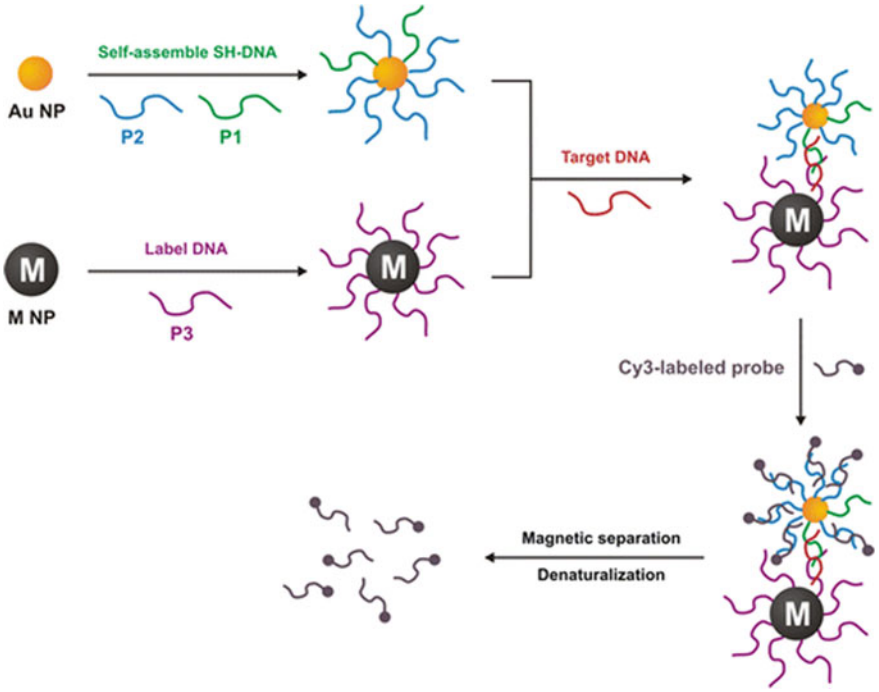

Fig. 12 Scheme of DNA detection based on fluorescence labeling and magnetic separation. Adapted from ref [121]. Copyright obtained from American Chemical Society 2012

3.7 Magnetorelaxometry

Magnetorelaxometry is a method for evaluating immunoassay [130]. The relaxation of the net magnetic moment of a system of magnetic nanoparticles after removal of a magnetic field is known as magnetic viscosity, and it can be measured by using magnetorelaxometry. The relaxation mechanism is mainly of two types. The First one is the Néel relaxation, in which the internal magnetization vector of a nanoparticle relaxes direction of the simple axis within the core. In Brownian relaxation, particles achieve rotational dispersion in a carter liquid. The different relaxation time of both Néel and Brownian relaxation helps to discriminate them [131]. Moreover, Brownian relaxation can occur only in liquids, while Néel relaxation does not rely on the distribution of the nanoparticles. Magnetorelaxometry can be used as an analytical tool for the evaluation of immunoassays because this technique helps to differentiate between the free and bound conjugates by their unlike magnetic behavior [130].

4 Conclusion and Future Prospects

The development of nanoscience and nanotechnology has led to the advancement in the research and technologies based on magnetic nanoparticles. The possibility of tailoring its physicochemical properties including biocompatibility has made it a promising candidate in pharmaceutical and biomedical fields. The applications such as disease therapy-extensively chemotherapy, drug delivery, MRI, tissue engineering, etc., make use of MNPs in a wider range. Still, the toxicity and side effects remain as a challenging problem in its development and yet to be investigated much. The toxicity of MNPs is multi-factorial and depends on its composition, surface characteristics, mode of action, dose, etc., which is case dependent also. Confidently, MNPs could open a new arena of research and application in the biomedical field with the increasing understanding on its interaction with living cells.

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Chapter 2
Surface Chemistry and Properties of Magnetic Nanoparticles

Anshida Mayeen, Anju K. Sajan, and Nandakumar Kalarikkal

1 Introduction

Magnetic nanoparticles are those materials whose particle size distribution was in nanodimensions and it can be manipulated by magnetic fields. Generally, magnetic nanoparticles are inorganic zero-dimensional materials with metal-based configuration. They may be either pure magnetic metals like nickel (Ni), cobalt (Co), iron (Fe), etc., or composed of magnetic bimetallic alloy like materials, or it is composed of magnetic oxides like spinel ferrites, inverse spinel ferrites, etc. Magnetic nanoparticles can be easily tuned by alternating current magnetic field and can be tailored for various applications [1–4]. Magnetic nanoparticles in nanometer regime have the ability to exhibit drastic intrinsic and extrinsic properties such as high saturation magnetization, less toxicity and high degree of biocompatibility. In this contest, magnetic nanoparticles possess wide range of applications in diversified fields such as industrial, environmental, analytical and biomedical [5].

Magnetic nanoparticles in the nanoscale possess drastic property change when compared to the bulk materials, and these behaviors can be attributed to the interplay of quantum, finite-size interactions with surface and interface. In particular, magnetic nanoparticles serve as powerful building blocks that have led to many nanotechnology applications in fields such as ultrahigh-density magnetic recording, biomedicine (e.g., guided drug delivery, and cancer treatment through

A. Mayeen · N. Kalarikkal
School of Pure and Applied Physics, Mahatma Gandhi University, Kottayam, Kerala 686560, India

A. Mayeen (✉)
Department of Physics, Thangal Kunju Musaliar College of Engineering, Kollam 691005, India

A. K. Sajan · N. Kalarikkal
International and Inter University Centre for Nanoscience and Nanotechnology, Mahatma Gandhi University, Kottayam, Kerala 686560, India

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hyperthermia or cell separation and purification) and magnetic resonance imaging (MRI) [1]. The key challenges are to understand how nanostructural features (such as topography, composition, crystallinity and surface chemistry) influence the physical properties of the nanoparticles (magnetic, electronic and so forth), and how this insight can be used to induce or improve their functionality in different applications.

1.1 Properties of Magnetic Nanoparticles

Magnetism is basically formed due to the orbital and spin movement of electrons, and its strength depends on the intensity of interaction among them. In some of the magnetic materials, the interactions between the atomic magnetic moments are not collective [3]. On the other hand, in some magnetic materials, the atomic moment interactions of other materials are comparatively strong, such that magnetic materials can be easily distinguished.

1.1.1 Magnetic Nanoparticles—Physical Properties

Magnetic properties are produced by movements of particles, both mass and electric charges. These particles may be electrons, holes, protons, and positive and negative charged ions. A magnetic dipole can be produced by spinning of electrically charged particle, and it is called a magneton. Ferromagnetic materials, magnetons are connected in groups. A magnetic domain denotes the volume of ferromagnetic material such that all magnetons are aligned along the same direction by their exchange interaction/force. Because of this, we can easily distinguish ferromagnetic materials and paramagnetic materials [3].

Generally, magnetic nanoparticles exhibit different magnetic behaviors in alternating current magnetic field and can be classified into the following categories

(1) Diamagnetic,
(2) Paramagnetic,
(3) Ferromagnetic,
(4) Antiferromagnetic,
(5) Ferrimagnetic.

2 Ferromagnetic Materials

Ferromagnetic materials possess a permanent magnetic moment even in the absence of an external magnetic field and possess high permanent magnetizations. Here, the magnetic domain in these materials has its own direction of magnetization; hence,

spontaneous magnetization will be not apparent in ferromagnetic materials, which have been exposed to the external magnetic field. When the magnetic field is applied, the domains in which the magnetic moments remain parallel will align in the direction of the applied field. Here, the spontaneous magnetization possesses several orders of magnitude than the applied magnetic field, and ferromagnetic materials possess very high permeabilities of almost of the order of 10^6 [3].

Here, the size-dependent magnetic behavior of the ferromagnetic material is determined by the domain structure of the ferromagnetic material. The interesting thing is that the size of the ferromagnetic material is reduced to a very lower range of the order of ~ 10 nm, and it becomes a single domain. These drastic changes in the magnetic behavior of the ferromagnetic materials are due to the size effects and its influence on the magnetic domain structure. It could be noted that that at a lower particle size, the ferromagnetic materials possess lowest free energy and uniform magnetization; on the other hand, magnetic nanoparticles having larger particle size possess higher free energy and non-uniform magnetization. The ferromagnetic nanoparticles with lower particle size exhibit single domains, while the other one possesses multidomains [3–5] (Fig. 1).

Based on the magnetic domain theory, the critical size of the single domain can be influenced by several features such as saturation magnetization, exchange forces, crystal anisotropy, shape of the magnetic nanoparticles and domain wall energy. Ferromagnetic behavior of the nanoparticles can be well studied using the magnetic hysteresis loop which is characterized by the following parameters, remanence and coercivity [3]. Also, the ferromagnetic property of the nanoparticles can be analyzed by observing the area of the hysteresis loop. It is found that as the particle size decreases lower to the critical limit, the area of ferromagnetic hysteresis loop was found to be small with increased coercivity.

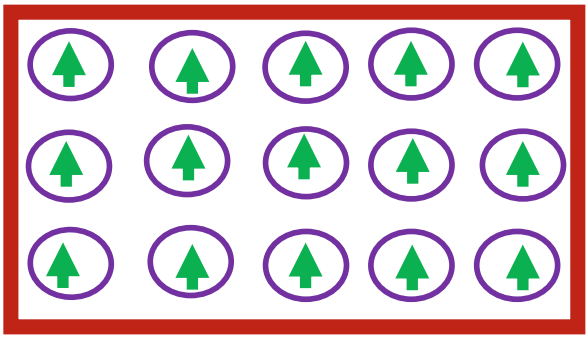

Fig. 1 Ferromagnetic materials in which magnetic moments are aligned along the same direction

3 Diamagnetic Materials

Diamagnetic materials are the materials that can be freely magnetized when it is subjected to a magnetic field. Here, the magnetization will be in the opposite direction to that of the applied magnetic field. Also, it could be noted that there will be no atomic dipoles present in these diamagnetic materials, and the resultant magnetic moment present in each atom will be zero because of the presence of paired electrons [3–7]. These diamagnetic nanoparticles can be strongly repelled by a magnet. In diamagnetic nanoparticles, the intensity of magnetization will be very small and negative and which is proportional to the magnetizing field (Fig. 2).

4 Paramagnetic Materials

Paramagnetic materials or nanoparticles are those materials in which they get weakly magnetized along the direction of the magnetizing field, when an external magnetic field is applied. They possess a permanent dipole moment or a permanent magnetic moment. But if the external magnetic field is removed, these magnetic materials will lose its magnetic properties. This behavior is attributed to the rearrangement in magnetic spins due to thermal motion [3, 8].

These paramagnetic materials possess unpaired electrons, and due to the presence of these unpaired electrons, the net magnetic moment of all electrons in an atom becomes zero, and as a result, atomic dipole does not exist in these materials. When an external magnetic field is applied, the atomic dipoles align along the direction of the external magnetic field, and this is the mechanism in which paramagnetic materials get magnetized in the presence of an external magnetic field (Fig. 3).

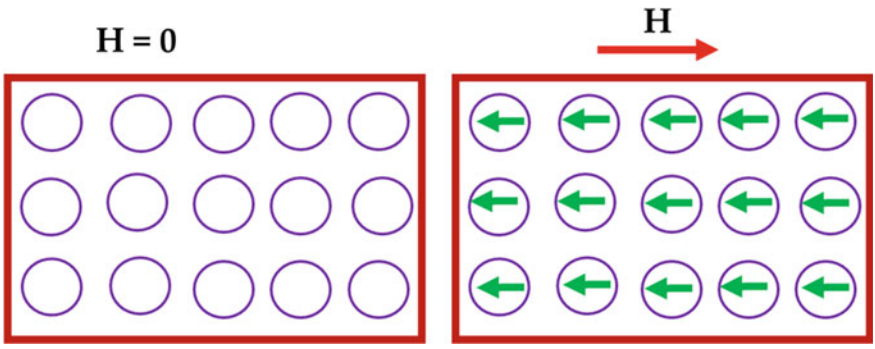

Fig. 2 Orientation of magnetic moments in the absence and presence of external magnetic field in a diamagnetic material

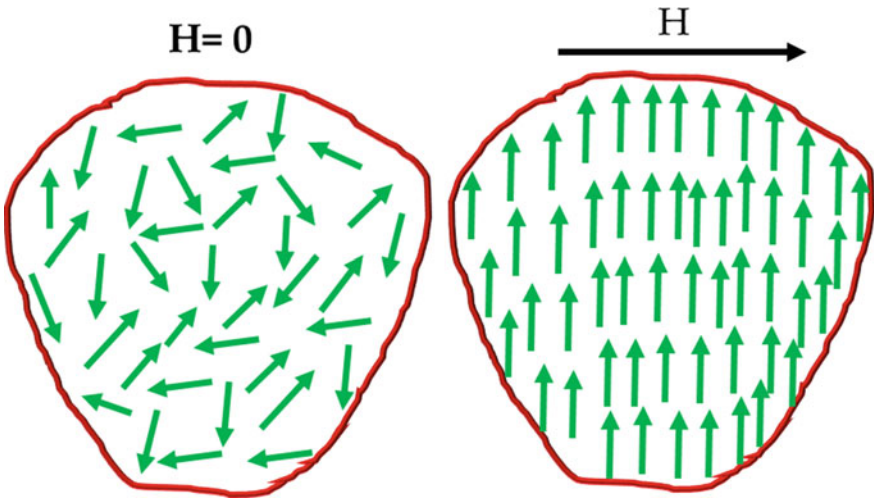

Fig. 3 Orientation of magnetic moments within a paramagnetic material in the absence and presence of external magnetic field

5 Ferrimagnetic Materials

In ferrimagnetic materials, the magnetic structure was composed of two different magnetic sublattices represented by A and B (cations) separated by oxygen atoms; here, the exchange interaction is controlled by oxygen anions. In ferrimagnetic materials, the magnetic momenta of A and B cations are not equal, and as a result, there will be a net magnetic moment. Ferrimagnetism is closely similar to the ferromagnetic materials. It exhibits almost all the properties of the ferromagnetic behavior like spontaneous polarization, hysteresis loop, remanence, Curie temperature, etc., but there will be a slight difference in magnetic ordering [3]. In ferrimagnetic materials, interactions are called indirect interactions or superexchange interactions (Fig. 4).

6 Antiferromagnetic Materials

Antiferromagnetism is similar to that of ferromagnetism; in the sense, the magnetism arises due to the collective phenomena that forms domains. In antiferromagnetic materials, the adjacent ions behave as tiny magnets, which spontaneously align themselves at a lower temperature in an opposite and antiparallel manner. Such that the material possesses no gross external magnetism [3]. Hence, it can be concluded that in antiferromagnetic materials, the magnetism from magnetic ions is

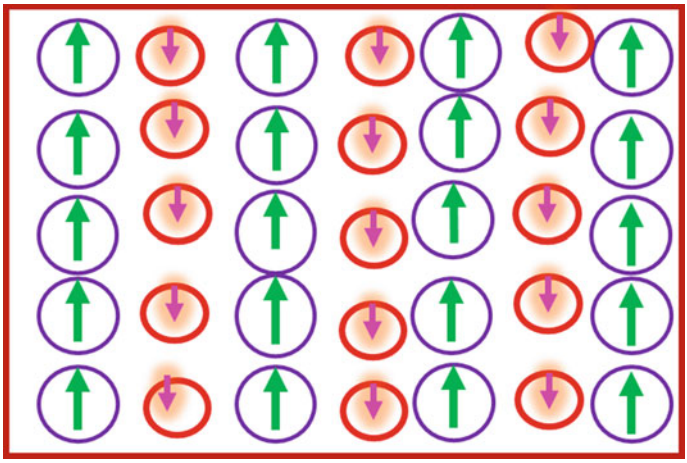

Fig. 4 Magnetic moment orientation in a ferrimagnetic material

oriented along one direction and is canceled out by the magnetic ions that are oriented along the other direction (Fig. 5).

7 Surface Chemistry of Magnetic Nanoparticles

Ferromagnetic or superparamagnetic nanoparticles possess large number of applications in various fields. In nanomedicine, these magnetic nanoparticles possess a significant role in magnetic resonance imaging, hyperthermia therapy, drug and

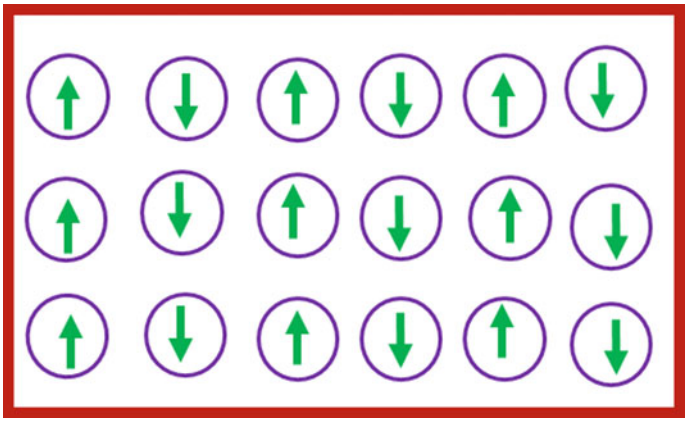

Fig. 5 Orientation of magnetic moment within an antiferromagnetic material

gene delivery, detoxification of biological fluids or immunoassays which are non-toxic. The superparamagnetic/ferromagnetic nanoparticles with high saturation magnetization and low coercivity were used for in vivo applications. Among the magnetic nanoparticles, two different classes of superparamagnetic iron oxide nanoparticles (SPIONs) were widely used, ultra-small iron oxide nanoparticles with average particle size less than 50 nm and iron oxide nanoparticles with average particle size ranging from 50 to 100 nm. Both of the above magnetic nanoparticles are composed of ferrite nanocrystals of magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3)—here Fe_3O_4-based particles having a large magnetic moment approximately of 92 emu/g and γ-Fe_2O_3-based particles having a magnetic moment ranging from 60 to 80 emu/gm. Other magnetic nanostructures involving composite, core–shell structures, etc., possess the value of magnetic moment ranging from 52 to 110 emu/gm [1].

The main concern regarding this is the high surface energy of these magnetic nanoparticles; since these magnetic nanoparticles have higher surface energy, the chances of agglomeration and aggregation of nanoparticles will be higher. This may affect the magnetic properties of the individual nanoparticles. The only solution for this is to functionalize these magnetic nanoparticles and hence reduce the surface energy of the system. For this surface modification of these magnetic nanoparticles with polymers, inorganic silica shells and bi-functional ligands like phosphonate or dopamine were used. For the biomedical applications, the targeting agents and drugs have to be easily integrated on the nanoparticle's surface [1, 3–5].

8 Surface Modification of Magnetic Nanoparticles

The major role of surface functionalization of the magnetic nanoparticles was to provide high degree of stability. If the nanoparticles possess low stability and higher chemical reactivity which creates health risks to the patients, different surface modification strategies were adopted by the researchers to address this problem [1].

8.1 Silica Shell (Silica Modification)

Silica coating over the magnetic nanoparticle is an efficient way to attain maximum stability for magnetic nanoparticles along with better biocompatibility. Silica-modified magnetic nanoparticles are suitable candidates for potential application due to the following facts that silica is chemically inert, low cost and optically transparent. For the silica shell coating over magnetic nanoparticles, alkaline hydrolysis of tetraethyl orthosilicate (TEOS) method is widely preferred [3].

8.2 Gold Shell (Gold Modification)

Gold is considered as a material of merit; because of its high chemical stability and biocompatibility, gold coating of magnetic nanoparticles was used in biomedical applications. Another interesting property of gold is that it possesses established reactivity with thiolated compounds. Gold-coated magnetic nanoparticles have gained huge attention in bioassays, since it combines both the properties of gold like high catalytic efficiency, high conductivity and optical properties like surface plasmon resonance along with magnetic properties of the magnetic nanostructures [1].

8.3 Catechol Functionalization

Catechol ligands are highly stable so that catechol functionalization is a better choice for the functionalization of magnetic nanoparticles. The metal catechol bond is very stronger with both σ- and π-donor bonding, which results in the formation of high stability of the complex. According to Xu et al., a general strategy is the usage of dopamine as a stabilizing material to graft the functional molecules on the surface of magnetic nanoparticles. The basic mechanism is that ligand exchange between the oleic acid and oleylamine stabilized magnetic nanoparticles with dopaminesuccinyl-nitriloacetic acid [1].

8.4 Polymer Functionalization

For medical applications of magnetic nanoparticles, polymer coating of magnetic nanoparticles was also preferred over the functionalization with small organic molecules. Polymer coating over these magnetic nanoparticles can be achieved by three different approaches

(1) Grafting to during the synthesis of magnetic nanoparticles,
(2) By ligand exchange,
(3) Grafting from by immobilizing an initiator onto the surface of magnetic nanoparticles.

For polymer functionalization of magnetic structures, initially, the polymers like dextran, chitosan, poly (ethylene oxide) (PEO), poly(imine), poly(acrylic acid), poly(vinyl alcohol), etc., were selected. Recently, the commercially available MRI agents (beside VOP 345) are coated with natural carbohydrate polymers. The main limitation of physically adsorbed polymers is the lack of stability [1].

9 Biomedical Application of Magnetic Nanoparticles

Magnetic nanoparticles with sizes less than 100 nm possess unique properties such as high surface-to-volume ratios, high reactivities, magnetic susceptibility, biocompatibility, low toxicity, stability, etc. Magnetic nanoparticles are promising tools in biomedical treatment such as cellular therapy, tissue repairing, targeted drug delivery, magnetic resonance imaging, hyperthermia and cancer treatment. Materials with high saturation of magnetization such as transition metals (Fe, Co, etc.) and metal oxides (e.g., Fe_3O_4, γ-Fe_2O_3) are considered for effective therapeutic treatments. To improve the versatility and efficiency, MNPs are surface modified by functionalizing with suitable materials. The main important characteristics of organic or inorganic magnetic nanoparticle that enable them to be used in biomedical field include:

i. Used as magnetic vectors as they can be controlled by means of an external magnetic field,
ii. Used as contrast images as they can be visualized,
iii. Heated in a magnetic field to trigger drug release.

9.1 Hyperthermia Cancer Therapy

Magnetic nanoparticles being highly specific avoid side effects of conventional chemotherapy in cancer treatments [6]. These can be used as heating mediators for cancer therapy by intracellular hyperthermia, or as drug delivery carriers. It is difficult to find a definition of hyperthermia not linked to cancer therapy.

The ability of some magnetic nanoparticle to convert the electromagnetic energy to heat makes it possible to use as a novel material for hyperthermia treatment. Magnetic nanoparticles injected to the extra cellular space of tumors create a temperature elevation and destroy the tumor cells. Activation of these nanoparticles as nanoheaters can be controlled by an oscillating external magnetic field. The (radiofrequency) radiation used to induce temperature is healthy and can penetrate to large extent in the body. Heat capacity defined as specific loss power depends on the particle size and properties (strength and frequency) of applied magnetic field. Heat generation Q is given by,

$$Q(r) = \mathrm{SLP} * C(r)$$

Hilger et al. experimentally showed that mouse model magnetic nanoparticles could produce temperature elevation up to 70 °C. Agarose gel having pore sizes ranging from 50 to 800 nm is used to introduce the magnetic nanoparticles into the tumor tissue as they mimic different types of tissue. Chen et al. [7] have experimentally proved that 3 and 4% agarose gel has a microstructure similar to hard

tissue, while the lower concentration gel has a porosity similar to soft tissue such as brain. Bani et al. in their studies have revealed that casein-coated MNPs have great potential as anticancer agent in hyperthermia cancer therapy [8].

The major challenge of conventional chemotherapy that the healthy tissues also are being affected by high temperature has been overcome by the MNP-hyperthermia. High sensitivity of tumor cells to temperature above 42 °C initiates the selective killing of tumoral cells. Magnetic nanoparticles that offer high magnetic saturation guarantee efficient heating in an oscillating magnetic field. Increase in particle size results in higher magnetic saturation, but beyond the critical size (superparamagnetic limit), magnetic nanoparticles become ferromagnetic, resulting in aggregation of these particles. Surface-functionalized iron oxide nanoparticles having good magnetic properties have achieved its requirements for hyperthermia cancer therapy. Surface functionalization plays a vital role in the hyperthermia performance, and sufficient surface modification improves mainly their specificity, and so, the more selective killing of target cancer cells will be achieved. Among different polymorphs of iron oxide Fe_3O_4 and γ-Fe_2O_3 find an immense position in biomedical field, these are being biocompatible, biodegradable and non-toxic (low dosage) [9].

9.2 Contrast Agents for Nuclear MRI

MRI is the most powerful non-invasive method used for diagnosis at high spatial resolution based on the principle of NMR. The ability of superparamagnetic MNPs to enhance the proton relaxation of certain tissue serves as contrast agents in magnetic resonance imaging. Apart from exhibiting better imaging performance, they offer grater versatility of multi-modal, stimuli-responsive targeted imaging [10]. In MRI, protons will align and precess around an applied external magnetic field. Upon application of a transverse radio frequency pulse, these protons will get perturbed from the field. The subsequent precession by which these protons return to original state is referred to as relaxation. Accumulation of magnetic nanoparticles in tissue enables contrast enhancement of MRI (changing signal intensity) by shortening both longitudinal (spin–spin) and transverse (spin–lattice) relaxation of nearby protons. The use of paramagnetic centers to reduce the relaxation time which in turn enhances the image was first reported by Bloch in 1948. Experimental studies done by Wang et al. give relevant knowledge that superparamagnetic iron oxides (SPIONs) are promising MNPs that are able to alter the spin–spin relaxation of water molecules and in turn enhance the negative contrast image [6]. Requirements of MNPs to be used as contrasting agents include the following:

1. Low toxicity,
2. Colloidal stability,
3. Little proclivity toward aggregation,
4. Controlled surface charges, etc.

Superparamagnetic nanoparticles are mostly derived from iron oxides and are functionalized using stabilizing agents to increase their multifunctional properties. These are effective probes in the magnetic field ranging 0.3–7 T. Chen et al. [11] reported the advantage of polyethylene glycol (PEG)-coated iron oxide nanoparticles as nanoprobes for magnetic resonance imaging (MRI) contrast agent. SPIONs are strong T_2 MRI contrasting agents over conventional Gd^{3+} based contrasting agents [12, 13], feridox, resovist, comdidex, etc. Iron oxide nanoparticles are degraded in liver and spleen and finally get integrated in the metabolic pathway. Inorganic nanoparticle-based multiphoton fluorescence probes have driven attention due to their enhanced resistance to photo-bleaching and relatively facile surface modification with functional molecules. Easily tunable emission wavelength along with its optical and chemical stability of quantum dots finds its advantage to be used as robust fluorescent tags in optical imaging [14]. Besides their low toxicity, manganese-doped ZnS nanoparticle has the ability to change the emission wavelength, which allows more light to escape from the tissues. Other than ZnS:Mn, InP/ZnS, $CuInS_2$/ZnS QDs are novel candidates for less toxic probes for imaging purpose [5].

Researches reported that SPION coated with natural rubber latex (NRL) and their incorporation in gelatin matrix has potential to be used as MRI contrast agents. As these MNPs are synthesized using green synthesis [15], it finds its importance in the present era as it minimizes the extent of pollution. Latex coating increases magnetization of MNPs, and increasing the latex concentration decreases the r_2/r_1 relaxivity ratio. Thus, latex is considered as efficient natural and biocompatible stabilizing agent for MNPs to use as contrasting agents in MRI

All in one multimodal nanoparticle (AION), e.g., Ag_2S-NP, IO-NP and DiR, in the hydrophobic core of phospholipid micelles has potential as a safe and effective multimodal contrast agent for a range of breast cancer imaging techniques [16].

9.3 Cell Separation

Cancer is a highly heterogeneous disease for which patients are given medical care based on their personal molecular phenotype [17]. Isolation and detection of the rare cancer cells are the most important factors that help in early diagnosis and treatment which reduces the number of cancer deaths. Surface functionalization of MNPs known for their cancer cell targeting helps to design effective immunoassays. In other words, MNPs act as cancer-associated biomarkers enabling molecular targeting. Cytokeratin is the most widely used biomarker for the detection of epithelial tumor cells in blood, bone marrow, lymph nodes, etc.

In order to understand various therapies of diseases and to design appropriate drugs, structures of cell membrane proteins and their response to cellular signals have to be figured out. Pillararenes, a class of supramolecular host, have attracted a lot of attention due to their unique host guest properties. Shu et al. in 2018 have successfully developed a new MPSE strategy to separate and enrich the membrane

proteins based on host–guest chemistry. MNP-P5 (per-phosphate pillar[5]arene coated on MNP) exhibited guest affinity along with magnetic response and thus has the ability to capture the targeted protein from protein mixture by host–guest interaction [18]. Simple synthesis, fast separation and good performance are the advantages of MPSE strategy of MNP-P5 over other methods

9.4 Drug Delivery

Efficient therapeutic action of drugs can be achieved only when they could accumulate at desired sites for required period of time in adequate concentration [19]. Drug delivered to desired tissue increases efficacy, minimizes side effects and avoids hurdles faced by drugs before reaching the site of reaction. Paul Ehrlich (Nobel Prize in 1908 for his work on immunity) proposed that if an agent could selectively target a disease causing organism, then the toxin for such an organism can be delivered to the site using the agent selectively, and the agent was named as "magic bullet." MNPs make the biological barriers slightly permeable for drugs or release the drugs at targeted sites after puncturing the barrier [16] and also protect the drug from fast degradation. This finds many opportunities in cancer therapy and in many other ailments. Surface-modified MNPs have high drug loading capacity and fast removal from the body fluids. MNPs coated with neutral or hydrophilic compound such as dysopsonins and PEG increase the circulatory half-life from minute to hours/days [20]. Coating (stabilizers) generates an interparticle repulsive force and thus prevents the aggregation and oxidation in the bloodstream. Investigations have proved that polymer-coated drug agents are 50% more efficient than intrinsic drug itself.

Nanoscale MNP protein hybrid is an excellent tool in implementing ocular drug in neuroprotection and therapy [21]. The surface chemistry of MNPs avoids the action of reticuloendothelial system (RES) and increases the half-life of drug in the bloodstream. Bovine serum albumin-coated magnetic nanoparticles have been investigated as novel carrier for curcumin (diferuloyl methane) abbreviated as CUR [22–25]. CUR that has been isolated from rhizome of turmeric has many clinical applications including in cancer treatment as it has the ability to decrease tumor growth. The drug loading capacity is given by the equation;

$$\%\mathrm{DL} = (\text{Mass of drug in nanocarrier}/\text{mass of nanocarrier}) * 100$$

Hoang et al. [23] in 2019 revealed that the effectively entrapped doxorubicin (DOX), an anticancer drug, in the core–shell system of SPION@HP (HP—heparin poloxamer) with a loading efficiency of 66.9 ± 2.7% can be used as an effective targeted delivery system for cancer treatment.

10 Conclusion

Magnetic nanoparticles are having a variety of promising applications spreading from modern electronic devices, sensors, high-density data storage media, targeted drug delivery and cancer diagnostics/treatment systems. This chapter describes an introduction to the properties and surface chemistry of magnetic nanoparticles. Also, it describes the functionalization of magnetic nanoparticles, applications of magnetic nanoparticles, etc. Different surface modification strategies were adopted by the researchers in order to reduce the surface energy and hence prevent the agglomeration of magnetic nanoparticles.

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Chapter 3
Magnetic Nanoparticles for Image-Guided Drug Delivery

Ruby Varghese, Namitha Vijay, and Yogesh Bharat Dalvi

1 Introduction

For last few decades magnetic iron oxide nanoparticle (MIONPs) are acquiring a great deal of attention from research fraternities around the globe due to their unique physiochemical properties and ability to function at the cellular and molecular level. This offered a potential platform for the field of nanotechnology to revolutionize the current diagnostic and therapeutic technique [147] (Fig. 1).

MIONPs are being actively investigated as the next-generation magnetic resonance imaging (MRI) contrast agents [21] and as carriers for targeted drug delivery. These applications are displayed by MIONPs due to enhancement of proton relaxation around the targeted or diseased site, which can be easily monitored and guided by imaging techniques. Among various MIONPs, superparamagnetic iron oxide nanoparticles (SPIONs) have been favored because of easy synthesis, biocompatibility, versatility with possible surface modifications and considerably less toxicity or no toxicity [40]. SPIONs make a unique MIONP due to its sensitivity towards the magnetic field and nanometric size (20–150 nm). As mentioned above, owing to various possibilities with surface modifications, a range of agents can be conjugated to the SPIONs like lactoferin [118], antitumor antibodies, small peptides [66] etc., and can be targeted to the diseased site or region of interest [87, 119]. These targeted agents can be easily monitored and guided to track tumor cells via MRI or to destroy tumor cells/diseased area by applying magnetic hyperthermia. Not only in cancer diagnosis but MIONPs are also used in monitoring early stages of endothelial inflammation (one of the initial symptoms of cardiovascular diseases) [148]. Despite the versatility in multimodal properties of SPIONs, an intensive study and proper understanding of it is needed before its introduction for clinical diagnostic utility. Two of the major concerns are the molecule structure of SPIONs

R. Varghese · N. Vijay · Y. B. Dalvi (✉)
Pushpagiri Institute of Medical Sciences and Research Centre, Tiruvalla, Kerala 689101, India

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Fig. 1 Importance of magnetic iron oxide nanoparticle in the field of nanotechnology to revolutionize current diagnostic and therapeutic technique

and its interaction with human body. For example, Iron oxide catalyses Haber–Weiss and Fenton reactions, which consecutively leads to the production of Reactive Oxygen Species (ROS) and, thereby leads to cellular damage. However, an intensive study brought an immense improvement in the utility of SPIONs in clinical diagnostics as MRI contrast agents (due to its ability to distinguish SPIONS in blood and those which were phagocytized by liver macrophages), drug delivery [41], in medical applications like Alzheimer's disease therapy [11], photodynamic therapy [131], cancer therapies [25, 35, 104, 151], detection of aflatoxin (IARC [45], bacterial diseases [42, 58] etc.

This review also discuss about theranostic platforms—an ever evolving system capable of delivering therapeutic and diagnostic agents. Ultimate goal of this research is to provide personalized medicine which is more efficient and non-toxic to the human body. In consistent with this goal, imaging techniques like MRI helps in remotely directing and monitoring the therapeutic drug to its destination.

The versatile functioning of MIONPs can be attributed to its MRI applications, hyperthermia properties and with ease which such particles can be fabricated to contain various functional moieties. Owing to the enhance permeability and retention (EPR) effects, as theranostic agents, MIONP-incorporated therapeutic drugs are able to be selectively accumulated at targeted diseased site [16, 53, 123]. Finally, tracking therapeutic drugs are carried out via imaging technique, and this principle is applied to image-guided drug delivery [125]. This review will provide an overview about physiochemical properties and pharmacokinetics of magnetic nanoparticles as MRI contrast agents and their applications as well as MRI-guided drug delivery including magnetic nanoparticles-based nanoplatforms.

2 Physiochemical Properties

When an external magnetic field (B_0) is applied, proton nuclei tend to align in the same direction to that of the magnetic field and begin to precess with a Larmor precession frequency and a net magnetic moment [16]. This external magnetic field, B_0, undergoes resonant excitation of magnetic moment on the application of resonant radio frequency pulse, which upon its removal causes the magnetic moment to gradually relax to equilibrium. In a biological tissue, MRI reconstructs 3D image of target anatomical site by recording the relaxation process. However, imprecise diagnostic information is obtained due to subtle contrast between the normal tissue site and diseased area. These subtle contrast differences can efficiently and effectively enhanced by the implementation of magnetic nanoparticle through the induction of magnetic dipole moment (μ) under an external magnetic field (B_0).

Two major advantages in using magnetic nanoparticle as contrast agents in MRI are (1) loadability: During synthesis of nanoparticle, the concentration of imaging agent can be controlled and (2) tunability of surface of nanoparticle: It has the potential to extent circulation time of contrast agent in the blood stream or target tissue of interest. Hence, it can be clearly used for molecular imaging especially MRI [27].

MRI contrast agents relies on iron oxide nanoparticles or ferrites, producing negative contrast in T_2-weighted images; or complexes belonging to lanthanide metals (especially gadolinium ions), providing positive contrast in T_1-weighted images.

Though intrinsic contrast is sufficient for MRI, but an enhancement of 40% in intensity of contrast tissue is observed with the administration of exogenous contrast agents [89]. Basically, MRI contrast agents are classified into paramagnetic or superparamagnetic materials. When radiofrequency pulse is stopped, protons will return back to their original alignment with the magnetic field. This is called as relaxation time which is categorized into longitudinal relaxation (T_1) and transverse relaxation (T_2). Major role of T_1 and T_2 is to reduce the relaxation time producing a better image for anatomical region [121]. Most of the MRI contrast agents affect

both T_1 and T_2. Depending on the magnetic property of core part of the particles, they are usually categorized into T_1 or T_2 contrast agents.

T_1 contrast agent consists of high spin lanthanide paramagnetic metal ions like gadolinium (Gd^{3+}), manganese (Mn^{2+}), and iron (Fe^{3+}) which cause a positive contrast by reducing T_1 relaxation time [12], while T_2 produces a darker state in T_2-weighed image and consists of magnetic iron oxide nanoparticle, i.e., SPIONs.

T_2—contrast agents, especially iron oxide, are quite preferred and have been used for biomedical utility over a period of 25 years. Hence, as compared to paramagnetic materials, SPIONs act as a better MRI contrast agents because it easily dephases magnetic relaxation of protons and shortens the spin-relaxation time (T_2). SPIONs are preferred due to their chemical stable nature under physiological conditions, low cellular toxicity and high magnetic moments [29]. SPIONs exhibit this property due to its greater magnetic susceptibilities and magnetic dipole moments as compared to its counterpart (paramagnetic material). Hence, upon the removal of external field (B_0), each individual domains exhibits Brownian forces by freely rotating with no magnetic remanence. This enables SPIONs to avoid self-aggregation [62], but due to ubiquitous Van der Waals force, it tends to aggregate back, hence surface of the nanoparticle needed to be coated preferably by polymers to facilitate its use in biomedical applications.

In general, shortening of T_1 (spin–lattice relaxation time) and T_2 (spin-relaxation time) causes corresponding relaxation rate to increase in $1/T_1$ and $1/T_2$ thus in shorter time producing hyperintense and hypointense signals. These characteristics maximize the magnetic moment of nanoparticle during its preparation [53]. The magnetic moments can be tuned by controlling various characteristics of nanoparticles such as shape, size, crystalline phase, and composition. On the basis of size, SPIONs are categorized into three (1) micrometer-sized paramagnetic iron oxide; (2) superparamagnetic iron oxide (diagnosis of hepatic disease and tumor detection) and (3) ultra-small superparamagnetic iron oxide (diagnosis–angiography and blood pool imaging). These magnetic moments are also influenced by doping with magnetically susceptible elements. Typically, two oxides of magnetic iron nanoparticles are considered for biomedical applications, mgnetite (Fe_3O_4) with a critical upper limit of 25 nm (for the observation of superparamagnetism) and maghemite (γ-Fe_2O_3) with a critical upper limit of 30 nm [61]. As mentioned earlier, these oxides are coated with polymers which are either amphiphilic or hydrophilic, charged or neutral, homopolymer or co-polymer, e.g., polyethylene glycol (PEG), chitosan, dextran, starch, polyvinyl alcohol (PVA), etc., and bioactive molecules or structures like liposomes [97, 120].

Superparamagnetism consists of an inverse spinel crystal structure with close packed cubic lattice formed by O_2 atoms with tetrahedral and octahedral sites occupied by Fe^{3+} and Fe^{3+}/Fe^{2+}, respectively (during B_0 magnetization electron hoping between Fe^{3+}/Fe^{2+} occurs at octahedral site) [123]. To improve magnetic properties, SPIONs are complexed with Mn, Fe, Co, and Gd to increase MRI contrast as well as currently been used as dual contrast agents [91, 113, 124, 150].

3 Pharmacokinetics

Fundamentally, the most important requirement prior to the synthesis of nanoparticle as contrast agent is to understand is its biological interaction and accumulation within the organ system. In the blood stream, protein opsonin bind to the surface of nanoparticles and underwent a process called opsonization. This process is commonly recognized and gets cleared from circulation by the mononuclear phagocytic system (MPS) (found in liver, spleen, and lymph nodes) and reticuloendothelial system (RES) (part of the body's immune system) [81, 79, 110].

Additionally, due to the increase ionic strength, magnetic property is altered and leads to aggregation. This may result into tissue toxicity (acute or chronic) like pulmonary embolism. Therefore, two factors are imperative for the construction of a biocompatible and reliable nanoparticle which can be responsible to develop a theranostic platform, viz. (1) minimum protein (opsonin) binding and (2) maximum half-life period in circulation. Hence, through adopting surface engineering, interference can be created with adsorption of protein (opsonin) to the surface of nanoparticle, producing "stealth" magnetic nanoparticles which will increases the likelihood to evade immune system and efficiently reach the target tissue [147].

Determining factors that enhances the efficacy of iron oxide nanoparticle to escape MPS and overcome vascular barriers are size, surface charge, shape, flexibility, coating and targeting [106]. According to Arnaud Vonarbourg, small nanoparticles are subjected to rapid renal clearance while large nanoparticles are confiscated by the phagocytic cells of liver, spleen and bone marrow [132]. With a hydrodynamic diameters, >200 nm nanoparticles are sequestered by MPS, while nanoparticles <20 nm escape phagocytosis and travel in the blood stream due to high circulation time of around 2 h [5, 9, 80, 90].

As uptake properties and clearance of nanoparticles by macrophage is different in normal and cancerous/inflammatory tissue, these factors can be considered as a useful diagnostic indicator. Thus, it has been used to diagnose liver metastasis [103, 130], splenic lymphoma [139], atherosclerosis [116, 117], metastatic lymph node [34, 141], stroke [115, 127], Glioblastoma [67, 88]. To target tumor tissue via EPR effect, hydrodynamic size of nanoparticle should range between 20 and 100 nm. Blood vessels of tumor tissue are leaky, and the pressure inside the tumor is remarkably high; therefore, in this case too, size plays a pivotal role. Nanoparticles with size below 40 nm or around 20 nm can readily pass through the leaky capillaries but can be washed out into bloodstream rapidly, while nanoparticles with a size limit of 100 nm slow down the migration via interstitial space and have the tendency to accumulate in tumor tissue. However, some studies also showed a restricted penetration into tumor mass. Thus, the above results clearly suggest that nanoparticle within a size limit of 20–100 nm is pharmacokinetically optimal for the rational design of theranostic agents in in vivo tumor targeting [75–79, 96].

Surface charge of nanoparticles also plays an important role in pharmacokinetic profile in the circulatory system. Charged nanoparticle has short blood circulation time due to opsonization hence subsequently eliminated from the circulation or get

accumulate which result into tissue embolism. Positively charged particles tend to bind with non-targeted cells or cause non-specific internalization or hemolysis. Thus, neutral or hydrophilic nanoparticle is preferred due to reduce possibility of opsonization, prolonged blood circulation and are more "stealthy" to complement system [18, 28, 123].

Although only a limited number of studies have been carried out to assess biodistribution of nanoparticle with varied geometries, still shape and flexibility of nanoparticles are also considered as essential and important physical parameters [61].

Coating can efficiently determine the fate of nanoparticle and also enhances biological interaction. It can also efficiently protect nanoparticle from the complement system, i.e., MPS and opsonin protein adsorption [76]. Major challenge in selecting a coating material is that it provides stability, biocompatibility and environment for biological interaction to the nanoparticle. These coating agents can be synthetic or natural monomers (e.g., bisphosphonates, mercaptosuccinic acid, etc.) or polymers (polyethylene glycol, polyvinyl alcohol, chitosan, dextran, etc.). Most of them enhances blood circulation time and prevents aggregation.

PEG is one of the common and FDA approved coating agents which is abundantly used due to its hydrophilicity, biocompatibility, cost effective, flexibility and lacks immunogenicity. Thus, it has been used in various clinical studies and imaging.

Studies have shown the role of coating agents in various biomedical applications including drug release, photodynamic therapy, chemotherapeutic drug delivery, and so on. Moore et al. synthesized X-ray-excited optical luminescent (XEOL) nanoparticles coated with poly(glycolide)-poly(ethylene) glycol to determine the amount of drug release into cells [82]. Grillo et al. [32] demonstrated that upon the application of external magnetic field, SPIONs conjugated with polymeric nanocarriers stimulate a control drug release. In another study by Ding et al. they synthesized multifunctional theranostic nanoparticle system (DSSCe6@Fe_3O_4 NPs) by loading iron oxide nanoparticle in redox-responsive chlorine 6 (Ce6)-conjugated dextran nanoparticles for dual-modality imaging and magnetic targeting [23], while Wang et al. prepared an iron oxide nanoparticle with dopamine modified hyaluronic acid for the delivery of hydrophobic chemotherapeutic drug [134, 137, 136]. Finally, bioconjugation of coating agents with other molecules such as antibodies, small peptides, aptamers, lectins and engineered proteins, proper selection is an utmost necessity.

4 MRI-Guided Drug Delivery

Magnetic nanoparticles (MNPs)/magnetic iron oxide nanoparticles (MIONPs) for image-guided drug delivery enables:

(1) Diagnostic Imaging: It provides a non-invasive approach to assess the biodistribution of theranostic agents.
(2) Drug delivery: Imaging/imaging guidance enables monitoring of controlled drug delivery at targeted site with accurate prediction of response or healing at real time.
(3) Novel therapeutics: With the use of advanced engineered liposomes, micelles, radiolabelled MNPs and various nanostructures with flexible shape or structures, a proper and controlled drug delivery as well as MR imaging can be achieved.

Following section discusses about magnetic hyperthermia, magnetic drug targeting, and applications of magnetic nanoparticle as theranostic agents or in theranostic platforms.

5 Biologically Targeted Magnetic Hyperthermia: Advantages and Limitations

In therapeutic context, hyperthermia means exposure of diseased site to an elevated temperature (i.e., 40–46 °C). The enzymatic actions of various cancerous cells can be altered, and apoptosis can be induced at this temperature in contrast to non-malignant/non-tumor cells [38] which remain unaffected. Magnetic hyperthermia (MHT) can be described as a mechanism in which magnetic nanoparticles, under the influence of external magnetic field can transform magnetic energy into thermal energy with consistent loss of hysteresis and relaxation [30, 107] (Fig. 2). This conversion of magnetic field energy into thermal energy under the reversal of magnetic field is caused by various processes occurring in particle system, i.e., (1) hysteresis, (2) Neel or Brownian relaxation, (3) eddy current and (4) frictional losses in viscous suspensions [37]. Recent reports suggest that hyperthermia is also favorable to various diseases apart from cancer which includes HIV, syphilitic paralysis and gonococcal infection [83]. Magnetic mediators are used for MHT which includes SPIONs, iron oxide-based nanoparticles such as MFe_2O_4 (where M = Co, Ni, Mn, Zn, Cu, Mg, etc.) and also lanthanum strontium magnetite oxide (LSMO) [55].

Two major role played by magnetic nanoparticle in MHT are:

(1) As magnetic heat induction utilizes radiofrequency electromagnetic waves, heat energy can be transferred to the localized magnetic nanoparticle which is 15 cm inside the living body [63]. Hence, MHT can be utilized to produce a unique drug delivery system.
(2) In an oscillating magnetic field, drugs complexed magnetic nanoparticle-based theranostic agents or fluorophores tagged magnetic nanoparticles through the heat-labile linker exhibit distantly controlled release via on-demand activation of the thermal energy generation [147].

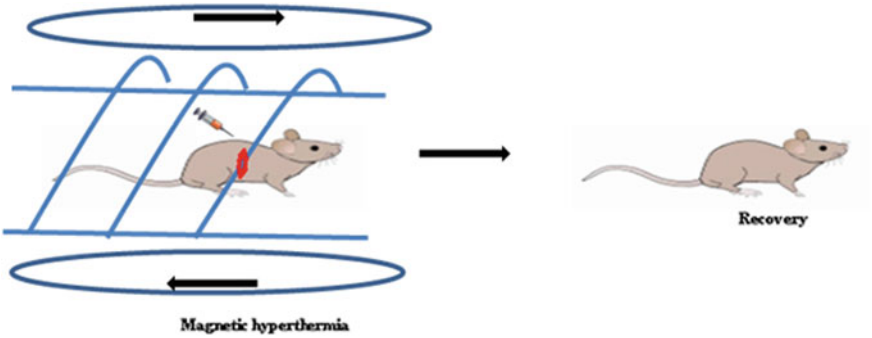

Fig. 2 Biologically targeted magnetic hyperthermia

6 Magnetic Hyperthermia and Its Role as Cancer Therapeutics

Hyperthermia (HT) can induce malignant cell death and act synergistically with radiotherapy and chemotherapy. It is described as chemosensitizer due to the generation of ephemeral disruption of blood brain barrier, increase blood flow, intrusion with DNA repair mechanism of malignant cells, damages transporters like ATP-binding cassettes, interferes with cellular metabolic activities of cancerous cells and can also withstand apoptotic pathways. HT plays a crucial role as radiosensitizer by interfering with DNA repair mechanism of malignant cells, suppresses AKT pathway and can easily damage hypoxic or plateau cells. The radiosensitization and chemosensitization properties displayed by HT may be due to its interference with DNA repair proteins of cancerous cells which ultimately result in protein denaturation [14].

According to National Cancer Institute, HT can be categorized into three: local hyperthermia (restricted to small area, e.g., tumor), regional hyperthermia (applied to larger part/tissue/organ, etc.) and whole body HT (applied to metastatic state) [112].

The hyperthermia modalities can be categorized on the basis of heating source and the nature of heated target from whole body to local and interstitial level. The basis of magnetic hyperthermia modalities is inserted heating sources in which macroscopic mediators are inserted inside the body by exact interventions, whereas micro- or nano-scale mediators injected in the form of colloidal dispersion of magnetic particles, i.e., called magnetic fluid hyperthermia (MFHT modalities can be classified on the basis of heating source and nature of the target site from whole body to localized area till interstitial level. Using clinical interventions, macroscopic magnetic nanoparticle mediators are inserted in the body cavity, whereas mediators at micro- or nano-scale are injected in colloidal dispersion form, and this mechanism is called as magnetic fluid hyperthermia (MFH). MFH is an experimental procedure which is performed on the basis of four strategies, i.e., (1) arterial

embolization HT (AEHT); (2) direct injection HT (DIHT) and (3) intercellular HT (IHT). The efficiency of this treatment depends on the magnetic properties and temperature homogeneity of magnetic nanoparticle mediators.

A number of pre-clinical and clinical studies have been explored to unravel the application and efficacy of MHT in vitro and in vivo conditions. Clinical studies are briefed in Table 1.

Jordan and co-workers synthesized dextran-coated MNPs to treat malignant glioblastomas in Fisher rats. Hyperthermia was induced by increasing temperature from 43 to 47 °C, and the resultant was increased survivability (i.e., 4.5 fold) in treated rats as compared to control rats [52].

In another study by researchers from Kansas State University, USA, evaluated the effect of bimagnetic nanoparticles (MNPs) (iron–iron oxide nanoparticle) combined with short external alternating magnetic field (AMF) against the growth of subcutaneous melanoma in C57/BL6 mice. An increase of 11 °C temperature was observed at subcutaneous level though actual temperature was not measured, but the resultant was very positive as significant regression in the tumor volume was observed in treated rats as compared to control group [10].

Berríos et al. induced hyperthermia via MFH to evaluate cytotoxic potential of bortezomib (BZ) in BZ-resistant and BZ-sensitive cancer cells as compared to hyperthermia using a hot water bath (HWH). The resultant was that MFH combined BZ treatment-induced cytotoxicity in both cell lines significantly than HWH under similar treatment conditions [3].

Rodriguez and co-workers synthesized SPIONs to deliver mild HT at a temperature of 42 °C in paclitaxel (PTX) pre-treated MCF-7 cells (sensitive and resistant to PTX), a breast adenocarcinoma cell line. It was observed that induced treatment significantly reduces cell survivability [105] as compared to control cells.

In an entirely different study, for the development of multifunctional nanoparticles combined with a near-infrared (NIR) plasmonic response and magnetic targeting, Tsai et al. constructed a rattle shape nanostructure by depositing double-layer silver/gold alloy on the surface of IONPs which exhibited a response for MRI, photothermal therapy, and magnetic guidance for hyperthermia. It is to be noted that these probes do not require chemotherapy drug due to its potential dual action as realized with PTT and hyperthermia [77, 100, 129, 133].

Extensive clinical research has been conducted to evaluate the application of hyperthermia, with a number of randomized trials and also to understand its potential as a single agent to improve the outcomes of various cancers without any adverse side effects. In Phase I, clinical trials magnetic nanoparticles with AMF was used against prostate cancer and glioblastoma. The outcomes were satisfactory as feasibility of the experiment approach was observed together with no post-treatment morbidity. Company like MagForce (based in Germany), carried out Phase-II clinical trial using MHT with sixty-six patients having recurrent glioblastoma and observed increased survivability. No major side effects were observed except worsening of motor disturbances, which may be caused or is due to disease progression rather than MHT [75]. Subsequently to the Phase II clinical trial, MagForce has conducted a randomized, controlled trial (DRKS00005476) to

Table 1 Few clinical trials utilizing MHT for cancer diagnosis

S. No.	Name and details	Country	Number of patient	Type of study	Application	Refernces
1	Radiofrequency captive heating device (Thermotran RF-8, Yamamoto Vinita Co., Osaka, Japan) (Power: 800–1500 MHz; Temp: 39.6–41.8 °C; Combined treatment: Radiotherapy)	Japan	40	Randomised clinical trial	Stage IIIB cervical carcinoma	Harima et al. [33]
2	Radiohyperthermia was provided using electromagnetic deep regional heating device (BSD medical corporation, Salt lake city, USA) (Temp: 42 °C) (Combined therapy: Chemo (Doxorubicin) and Radiation)	Germany	59	Phase-II clinical trial	Soft tissue sarcomas (High-risk)	Issels et al. [47]
3	BSD 2000 with Sigma 60 or MAPA applicators at frequencies of 60–140 MHz (Temp: 43 °C) (Combined therapy: Radiation)	US	35	Phase II clinical trial	Soft tissue sarcomas	Maguire et al. [73]
4	Thermochemotherapy by means of Synergo® (Medical Enterprises, Amsterdam, The Netherlands) (Temp: 42 °C) (Combined therapy: Chemotherapy-mitomycin)	Multicentre	83	Randomized controlled trial	Non-muscle-invasive bladder cancer (NMIBC)	Colombo et al. [19]
5	55 °C Curie temperatured thermoseeds (ATI medical, San Diego, CA, USA) (Temp:) (Combined therapy: Radiation)	Germany	57	Phase-II	Prostrate cancer (Localized)	Deger et al. [22]

(continued)

Table 1 (continued)

S. No.	Name and details	Country	Number of patient	Type of study	Application	Refernces
6	Microwave transurethral applicator (the Synergo® system SB-TS 101; Power: 915 MHz) (Temperature: 41–44 °C) (Combined therapy: Chemotherapy-mitomycin)	Multicentre (Israel, The Netherlands, Austria, Italy, France and Belgium)	41	Randomised trial	Intermediate or high risk superficial transitional cell carcinoma of the bladder	Van der Heijden et al. [36]
7	Microwave spirak strip applicators (Power: 433 MHz and Temp: 43-55 °C) (Combined therapy: Radiation therapy)	US	109	Randomised trial	Superficial tumors	Jones et al. [51]
8	Magnetic fluid MFL AS (MagForce Nanotechnologies AG, Berlin, Germany) (Temperature: up to 41 °C)	Germany	10	Phase I trial	Pancreatic cancer (Recurrent)	Johannsen et al. [50]
9	Magnetic fluid MFL AS (MagForce Nanotechnologies AG, Berlin, Germany) (Temperature: up to 41 °C) (combined with radio and chemotherapy)	Germany	22	Randomised trial	Carcinomas (Rectal, Cervical, Prostrate and Ovarian) and Sarcomas (Chondrosarcoma, Rhabomyosarcoma and parapharyngeal)	Wust et al. [143]
10	Magnetic fluid MFL AS (MagForce Nanotechnologies AG, GmBh, Germany) (Temperature: up to 48 °C) (Combination therapy: with brachytherapy)	Germany	1	Clinical trial	Prostrate cancer	Johannsen et al. [49]

(continued)

Table 1 (continued)

S. No.	Name and details	Country	Number of patient	Type of study	Application	Refernces
11	Magnetic fluid MFL AS (MagForce Nanotechnologies AG, Berlin, Germany) (consists of aminosilane coated SIONPs (core diameter: 15 nm) dispersed (Combination therapy: Radiation therapy) (Temperature: 43 °C) in water, with an iron concentration of 112 mg/ml.)	Germany	14	Randomised trial	Glioblastoma multifome	Maier-Hauff et al. [74]
12	Synergo® system SB-TS 101 is used to deliver local microwave induced hyperthermia and intravesical chemotherapy (Combination therapy: Chemotherapy-mitomycin) (Power: 915 MHz and Temp: 41–44 °C)	Multicentre	51	Phase II trial	BCG-failing carcinoma in situ (CIS).	Witjes et al. [142]
13	BSD-2000 hyperthermia system (BSD medical corporation, Salt lake city, USA) (Temp: 42 °C) (Combination therapy: Chemotherapy-Doxorubicin)	Europe and North America (Germany, Norway, Austria and US)	341	Randomized, Phase-II, Multicentric	Soft tissue sarcomas (High-risk)	Issels et al. [48]
14	Modified Thermatron, a radiofrequency (RF) machine (Power: 8.2 MHz; temperature: 42.3–44 °C (Combination therapy: Radiation)	India	56	Randomised trial	Head and neck cancers	Huilgol et al. [43]

(continued)

Table 1 (continued)

S. No.	Name and details	Country	Number of patient	Type of study	Application	Refernces
15	Local external microwave hyperthermia using WE2101—a microwave hyperthermia system (Yuan De Biomedical Engineering, Beijing) (Power: 915 MHz and temperature: 42.5–43 °C)	China	180	Phase-III	Nasopharyngeal cancer	Hua et al. [39]
16	Thermochemotherapy by means of Synergo® (Medical Enterprises, Amsterdam, The Netherlands) (Combination therapy: Chemotherapy-mitomycin) (Temp: 42 °C)	Multicentre	83	Randomized controlled trial	Non-muscle-invasive bladder cancer (NMIBC)	Colombo et al. [20]
17	Electromagnetic heat applicators (BSD medical corporation, Salt lake city, USA) (Temperature:) (Combination therapy: Radiation Therapy + Chemotherapy Cisplatin; etoposide and ifosfamide)	Germany	44	Open-label, non-randomised, single-institution, phase 2 study	Refractory or recurrent non-testicular malignant germ-cell tumours	Wessalowski et al. [140]
18	Hyperthermia device (Synergo system; Medical Enterprises Europe B.V., Amstelveen. The Netherlands) (Combination therapy: Chemotherapy) (Temp: 42 °C)	Multicentre (Israel, The Netherlands, Austria, Italy, France and Belgium)	190	Controlled, open-label and multicentre trial	Non-muscle-invasive bladder cancer (NMIBC)	Arends et al. [8]

evaluate the safety and efficacy of their products (NanoTherm® aminosilane-coated ferrofluid: NanoTherm® monotherapy and NanoTherm®) in combination with radiotherapy versus radiotherapy alone in recurrent/progressive glioblastoma. The study is closed, and reports were submitted to the official bodies [71, 72].

However, several limitations need to be resolved before this technology is used by clinicians, and they are:

(1) Though HT can induce cancer cell death, it is not very effective as single agent as it lacks specificity and develops thermotolerance in many cases. However, HT concomitantly with radio or chemotherapy potentiates their efficacy.
(2) Heterogenous outcomes at clinical trials were observed due to differential heating protocols which adversely affects the bystander (non-tumor/non-malignant) cells.
(3) Intratumoral delivery of MNPs is restricted to localized tissue and is more invasive than existing techniques.

7 Magnetic Drug Delivery

Under the influence of external magnetic field, magnetic nanoparticle can be directed to deliver drugs at target site via magnetic attraction [9]. This type of drug delivery is called as magnetic-targeted carrier (MTC) drug delivery technology. Rather utilizing biological mechanisms, MTC depends on or follows physical force of magnetic field to deliver drug via arterial wall into the diseased site (Fig. 3). It results into retention and localization of drug at desired site, even after the removal of external magnetic field. Drugs uptake in magnetic drug delivery is carried out through various processes such as conjugation [15, 99], interactions like hydrophobic interactions [17], absorption into the porous structures [54], etc.

Modern nanocarriers are built for maximum positive outcomes with minimum or negligible side effects. Nanocarriers are divided into organic (polymer-based nanocarriers, micelles, liposomes, vesicles, dendrites, carbon nanotubes) or inorganic and metallic (quantum dot, mesoporous, silica nanoparticles and SPIONs) [68]. While the drug release by these carriers are triggered by various factors such as change in pH [134, 137, 135, 138], mechanical forces [144], near-infrared (NIR) irradiation [136, 152], chemical reduction [7], high-intensity focused ultrasound HIFU [84] and MHT [17].

These nanocarriers can be prepared using laser pyrolysis [98], microemulsions [114], and sol-gel processes [149]. While thermal decomposition [101, 145, 146] and coprecipitation [59, 95] are the two main routes of synthesis [70].

MTC drug delivery technology has various applications which includes chemotherapeutic drug delivery, targeted delivery to brain, site-specific pulmonary drug delivery and in various biotechnological applications. MTCs have been used in cancer therapy for decades especially to mitigate most important and primary

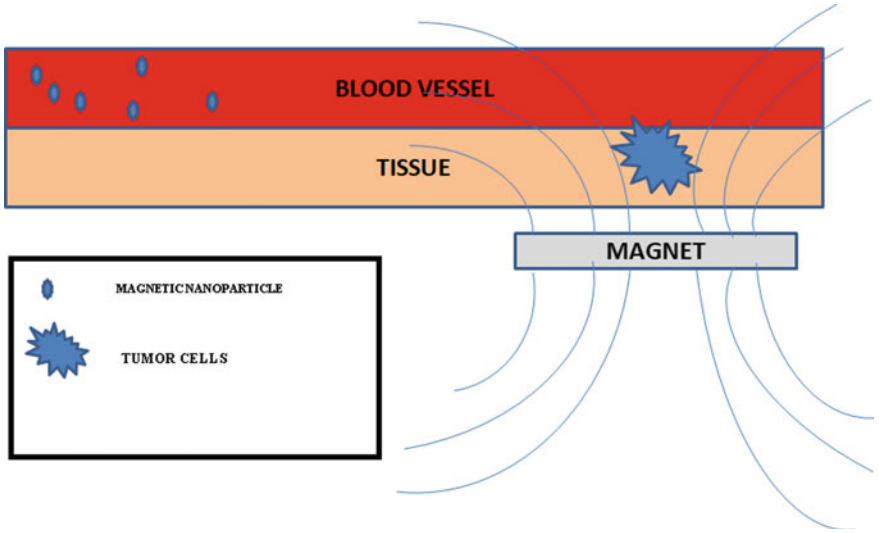

Fig. 3 Schematic representation of magnetic nanoparticle drug delivery systems for targeting tumor

drawback of chemotherapeutic drugs, i.e., lack of specificity toward tumor cells and toxicity to normal cells.

Clinical advantages in using MTC drug delivery technology are as follows (Häfeli et al. 1997):

(1) Probable decrease in local tissue clearance (blood flow).
(2) Endothelial diffusion into interstitial space against interstitial pressure gradient.
(3) Restriction of any degree of systemic distribution.
(4) Sustained and increased concentration of drug delivery in proximity of tumor.

Similarly, various obstacles are there in using MTC drug delivery technology which includes the following [24]:

(1) External magnetic field should be of strong gradient neither there is quite a significant chances of systemic distribution.
(2) Potential for embolization: Accumulation and restriction of particle in the blood vessel.
(3) Unsurety with respect to the depth in which magnetic guidance system may function.

However, with modern technology and various modifications into MTC has been developed into one of the most promising strategies for the augmentation of the imaging-guided delivery and the therapeutic action at pre-clinical and clinical level.

Alexiou et al. [2] synthesized SPION–mitoxantrone (MTX) complexes with a coating of starch polymer ($\sim$100 nm in diameter) for the treatment of VX-2

squamous cell carcinoma. The polymer helps in promoting binding and stabilization of chemodrug. Intra-arterially infused MTC (20 and 50%) into rats remitted the tumor completely with no adverse effects as visualized by MRI. On other hand, the MTX drug alone via intra-arterially route do not regressed the tumor and decrease the survivability. This result suggests the efficacy of the SPION–mitoxantrone (MTX) complex to potentiate the anti-cancerous ability of MTX [2].

Transfer of drugs across the blood brain barrier (BBB) is a challenging approach which can be overcome by transport of magnetic nanoparticles across the BBB aided by an extra cranially applied external magnetic force [126]. Hence, an attempt to deliver drugs like antiretroviral drugs has been carried out using magneto liposomes in an in vitro condition. Saiyed and co-workers developed a liposomal nano-formulation called as 3′Azido-3′deoxythymidine-5′-triphosphate (AZTTP) to evaluate its potential in delivering the MNP across an in vitro BBB model aided by external magnetic field. The results showed that transmigration of AZTTP across BBB was threefold higher than free AZTTP and a significant twofold uptake of AZTTP by monocytes was also observed [111].

Lübbe et al. [69] conducted first clinical trials of magnetic drug targeting. In Phase I, clinical trial, patients with advanced and unsuccessfully treated cancers or sarcomas were provided an appropriate doses and standardized the tolerance rate to epirubicin-bound magnetic fluid in fourteen patients. Each of them received different courses of magnetic drug targeting, which consisted of infusion of epirubicin-bound magnetic fluid with increasing doses (5–100 mg/m^2) and 60–120 min exposure to magnetic field. Magnetic fluid was able to target the chemotherapeutic drugs to target in about half of the patients with no adverse effects. However, organ toxicity associated with epirubicin appeared at doses greater than 50 mg/m^2. This trial showed the potential safety, effectiveness and practicality of magnetic drug targeting. However, due to many shortcomings like limited reduction, hematological side effects and magnetite accumulation in the tumor (which in variable degree), thus required a major improvement for the successful implementation of this technique.

Amanzadeh et al. [4] synthesized SPIONs which is conjugated with quercetin in a sole aim to improve memory and learning ability of healthy normal rats. Quercetin is a flavonoid which is known to protect neurons against the oxidative stress and apoptosis [1] but quercetin has a low bioavailability as demonstrated by various in vivo studies to induce long-term potentiation (LTP). It is cellular mechanism where synaptic plasticity of neural cells is strengthened and which causes preservation of memories. Hence, Quercetin conjugated SPIONs improvement in learning and memory of rats as revealed by Morris water maze (MWM) accompanied by increased bioavailability. As well as Quercetin bind to various proteins like RSK2, MSK1, CytC, Cdc42, Apaf1, FADD, CRK proteins causes improvement in learning and memory due to prevention of apoptosis. Hence, SPIONs increase bioavailability and LTP as compared to control [4].

8 Theranostic Platforms

In addition to the magnetic hyperthermia and MTC drug technology, a number of theranostic platforms have been studied for concurrent non-invasive detection of target sites, selective drug delivery, assessment of biodistribution of drug and monitoring of therapeutic responses at real time. Theranostic platforms have proven to be a reliable system for adequate understanding of proper accumulation of drugs at tumor site or region of interest. It is achieved either via EPR-mediated passive drug targeting or ligand-mediated active targeting which provides a potential rationale for continued development.

Zheng et al. [152] synthesized superparamagnetic iron oxide nanoparticles complexed with hyaluronic acid and C16 micelles followed by encapsulation of anti-cancer agent docetaxel to develop multifunctional micelles. This micelle is easily taken up by the tumor cells due to the presence of HA which binds to the CD-44 receptor commonly over expressed in various types of cancerous cells as compared to normal cells [64]. Cellular uptake of micelles carried out via CD-44 receptor-mediated endocytosis and was enhanced by the presence of a magnetic field. Thus, it creates a favorable environment for proper and definitive MR images as well as drug release was activated by NIR irradiation.

In a current study, Mu et al. developed a stem cell membrane-coated magnetic nanoparticle for image-guided photothermal therapy and gene therapy. These researchers synthesized mesenchymal stem cells membrane-coated Fe_3O_4@PDA-siRNA@MSCs, SiRNA has been used for gene therapy and gene silencing of PIK1 (phosphatidyl inositol 4-kinase, plays an important role in cancer progression). Study was aimed to evaluate efficiency of nanoparticle in gene therapy, gene silencing and ultimately inhibition of cancer progression. Polydopamine (PDA)-coated Fe_3O_4 nanoparticles are employed as photothermal (PTT) therapeutic anti-cancer agent owing to their outstanding near-infrared (NIR) performance and increased photothermal conversion efficiency [31, 86] to bind molecules like DNA [65] due to the presence of multiple functional groups. Mu and co workers demonstrated that expression of Plk1 gene in DU145 prostate cancer cell line following the delivery of siPlk1 through Fe_3O_4@PDAsiPlk1@MSCs nanoparticles were significantly decreased as compared to naked siPlk1 or control Fe_3O_4@PDA-siRNA@MSCs nanoparticles as revealed by molecular techniques RT-PCR and western blotting. Inhibition of cancer cell by Fe_3O_4@PDA-siPlk1@MSCs nanoparticles was followed via apoptosis as evaluated by flow cytometry. Intravenal injection of Fe_3O_4@PDA-siRNA@MSCs to the BALB/c nude mice bearing DU145 xenograft tumors displayed tumor darkening effects in T_2-weighted MR images after 24 h of injection. Clearly concludes its efficiency as MR imaging probe. In addition ICP-AES showed higher tumor accumulation capability of Fe_3O_4@PDA-siRNA@MSCs as compared to Fe_3O_4@PDA. Furthermore, evaluation of Fe_3O_4@PDA-siPlk1@MSCs nanoparticles together with laser therapy to

suppress tumor growth was observed and resultant was 60% reduction in tumor volume with no weight loss as compared to Fe_3O_4@PDA-siRNA@MSCs (40% reduction). Also, H&E staining of Fe_3O_4@PDA-siPlk1@MSCs nanoparticles demonstrated complete destruction of tumor cells, and TUNEL assay revealed that high percentage of cancer cells undergo apoptosis as compared to other controls. The findings suggested that Fe_3O_4@PDA-siPlk1@MSCs NPs efficiently enhanced tumor-targeting capability owing to its mesenchymal stem cell coating, with less toxicity which make it as an efficient biocompatible nanocarrier for cancer therapy [85].

Photodynamic therapy (PDT) is a type of technique which involves the uptake of a photosensitizer by cancer cells followed by photoirradiation to activate the sensitizer. This technology improvises the survivability and offers local treatment [57, 122]. However, this therapy holds a disadvantage of prolonged cutaneous photosensitization which can be overcome by encapsulating photodynamic agents in nanoparticles. Reddy et al. [102] synthesized multifunctional polymeric nanoparticles carrying both photosensitizers and MRI contrast agents for brain tumor-targeted therapy as well as tracking of therapeutic responses. These researchers synthesized photofrin- and iron oxide-encapsulated polyacrylamide nanoparticles. This nanoparticle was conjugated with PEG for stability, and for tumor vasculature targeting F3 peptides was used. The results showed that after 8 days of nanoparticles administration, T_2-weighted MRI with color overlays representing an obvious diffusion in coefficient values for tumors in a representative animal was observed. PDT-induced changes in tumor diffusion values were analyzed by diffusion MRI [108]. Furthermore, it was observed that animals treated with F3-targeted nanoparticles showed an increase in tumor diffusion values ($\sim$40%) and showed a high diffusion value after 40 days which is an indicative of cystic cavity. Finally, these results clearly demonstrated that treatment with F3-targeted nanoparticles have shown increased survivability demonstrating efficiency and versatility of this technique.

In addition to photodynamic therapy, dendritic cell (DC)-based immunotherapy has also displayed a potent therapeutic strategy against human malignancies [6, 109]. Nanoparticles are an excellent candidates for delivering antigens into dendritic cells due to their large surface areas which has a potent to incorporate multiple therapeutic agents in spite of which their clinical application is limited due to cytotoxicity [13]. Inomistova et al. developed mouse spleen dendritic cells complexed with iron oxide nanoparticles. DCs were intradermally injected to tumor bearing mice. Cytotoxic assay revealed non-toxic nature of nanoparticle. Animals administered with DCs and exposed to magnetic field showed a 1.7 times decrease in tumor metastases as well as decreased expression of FOXP3 in lymph node and IL-4 in spleen as compared to control [46].

9 Conclusion

A tremendous amount of investigations have been undertaken to develop MRI-guided delivery system, owing to their incredible physiochemical and pharmacokinetic properties; this system provides an immense opportunity for the non-invasive assessment of pathological site, detection of drug accumulation at diseased site and real-time prediction of therapeutic response. Additionally, owing to their excellent intrinsic magnetic properties, magnetic nanoparticles have been used as MRI contrast agents. Additionally, surface modification by a range of different organic molecules including surfactants, polymers and inorganic materials has the potential to improve the stability and biocompatibility of magnetic nanoparticles. This provides an enormous opportunity to deliver peptides, antibodies, aptamers, therapeutic agents at targeted site as well as an early stage diagnosis of disease.

However, it is noteworthy that despite Food and Drug Administration's approval and commercialization of iron oxide nanoparticle-based bioprobes for hyperthermia and MRI, clinical trials for magnetic drug delivery received less attention [77, 129, 133]. It may be due to many reasons including lack of proper understanding of the drug delivering magnetic nanoparticles into the depth of the human body, uptake by RES due to inefficient coating (provided with proper assortment of coatings, this issue can be nullified), specificity of targeting moieties, inclusion of proper surgical interventions for more precise understanding of interaction between nanoparticle and biological environment. Hence, not only physicists, engineers but also intervention of clinicians/surgeons may help in making magnetic nanoparticle as an efficient translational theranostic agent (i.e., from bench to bed side). Hence to conclude, MRI-guided drug delivery system opens the door for practitioners to avail real-time feedback and improve the balance between efficiency and toxicity of targeted interference.

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Chapter 4
Magnetic and Fluorescent Nanogels for Nanomedicine

Vineeth M. Vijayan, Bernabe S. Tucker, John P. Bradford, and Vinoy Thomas

1 Introduction

The field of nanotechnology has been exponentially advancing since the early 2000s. Bill Clinton excitedly proposed doubling the NSF budget in January of 2000 for the research into nanotechnology by supplying 475 million dollars [1]. Since that time the amount of research and money that has gone into nanotechnology has allowed for it to become its own subject and component in science. Nanotechnology is at the interface of biology, chemistry, physics, and engineering and was the term was first termed in 1974 as the handling of molecules on the nanoscale [2]. Application of nanotechnology is finding using in several fields of today such as energy, medicine, food packaging, water treatment, and the environment [3–7]. Below in Figs. 1 and 2 show not just the nations who publish the most research on the topic, but also the amount of money spent on nanotechnology by the top spenders globally as given by Statnano and the Congressional Research service, respectively.

The increase in money and quantity of publications is resulting in several categories of technology being affected. Traditionally speaking, as science progresses society becomes the beneficiary of that progress because basic needs, such as food, water, shelter, etc. become either more plentiful or easier to access. As needs are met, to further improve the quality of life, the next step would be to make everyday

V. M. Vijayan · V. Thomas (✉)
Center for Nanoscale Materials and Biointegration, University of Alabama at Birmingham, 1300 University Blvd. CH 386, Birmingham, AL 35294, USA
e-mail: vthomas@uab.edu

V. M. Vijayan · B. S. Tucker · J. P. Bradford · V. Thomas
Polymers & Healthcare Materials/Devices, Department of Material Science and Engineering, University of Alabama at Birmingham, 1300 University Blvd. CH 386, Birmingham, AL 35294, USA

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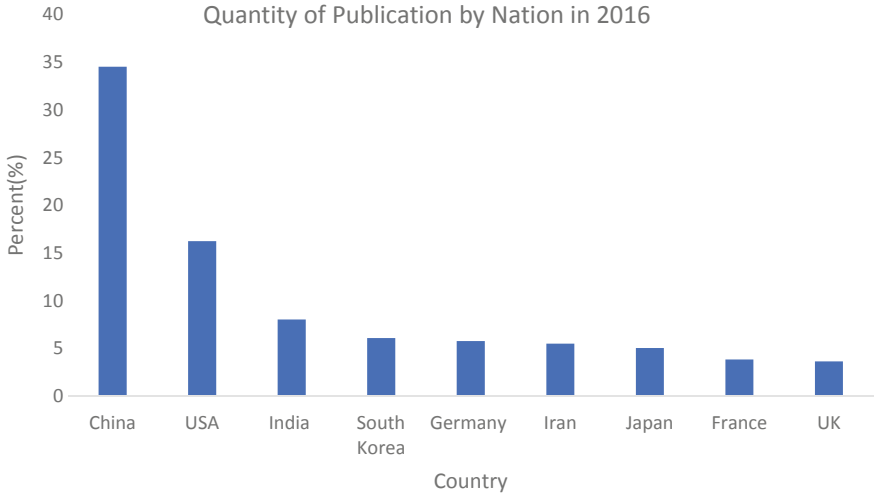

Fig. 1 Publications that came on the topic of nanotechnology based on quantity in 2016 by the top nations researching said topic. Data from Stat nano, http: statnano.com/news/57105

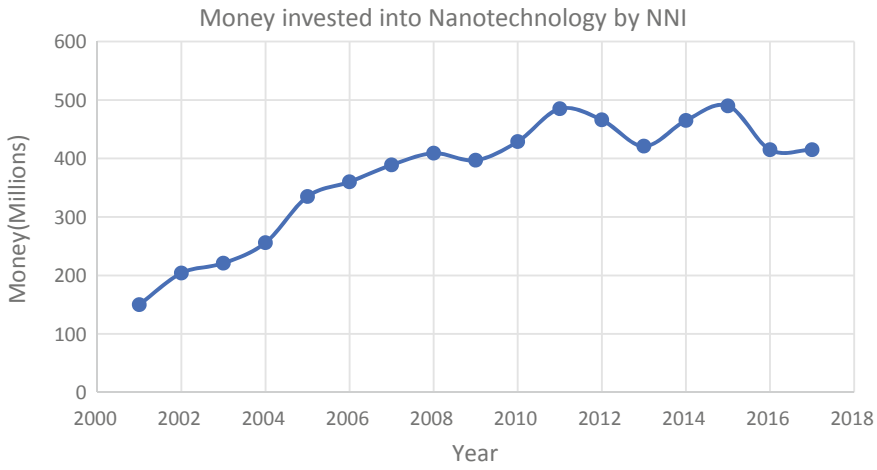

Fig. 2 An increase of funding given to the NSF by the NNI. Data from nanotechnology: a policy primer. 2016

task less time consuming, cost effective, and energy efficient. Nanotechnology can be viewed through the lens of having made everyday necessities more accessible and tasks done more efficient. Many fields are seeing continual growth because of nanotechnology, and a few fields are being affected are energy, technology, and medicine.

1.1 Role of Nanotechnology in Energy

As carbon emissions continue to rise annually, an Earth that is no longer inhabitable becomes less like a science fiction movie and more realistic. Increased industrialization has in most cases equated to an increase in economic success for countries; however, with this increase in industrialization also has called for an increase in energy usage [8]. Traditionally, energy has come from nonrenewable sources, such as oil, gasoline, coal. These sources, however, produce greenhouse gases that accelerate detrimental climate change. By changing to renewable energy sources such as solar, wind, rain, waves, geothermal heat, biomass, etc., the greenhouse gas production is significantly reduced, and there is an economic benefit that pairs with switching to renewable energy sources [9, 10]. The use of renewable energy sources offer these obvious advantages, but the problem with the most common methods of creating renewable energy sources stems from dependency on a specific climate need, but nanotechnology research in each of some of the different methods has proven to be effective in increasing the efficiency of energy storage and usage making these methods more practical for everyday use. An example of some of the research being done in the production of solar energy as a basis of substitution in the stead of nonrenewable energy is the mimicking of photosynthesis to create renewable clean energy [11–15]. Artificial photosynthesis converts base materials like water and carbon dioxide into chemicals such as hydrocarbons as a result producing energy [11]. For this system to work, both a successful conversion of solar power and an efficient conversion of water and carbon dioxide to fuels are necessary [11]. Using nanoclusters that have the ability to capture sunlight is specifically one way that nanotechnology is being utilized in the effort for production of cleaner energy. The use of surface modification of nanoparticles such as gold and fullerenes has been utilized in this effort to successfully convert light energy and increase efficiency of absorption of the visible region of sunlight for the transfer of energy and electrons [12, 14].

1.2 Role of Nanotechnology in Medicine

Nanotechnology as it pertains to medicine was first described by the late great Physicist Richard Feynman when he gave his famous, “There’s plenty room at the bottom” talk at Caltech in 1959. At this seminar, he described making tiny machines that have the capabilities of maneuvering at the size scale of biologic cells, and even goes as far as correctly foretelling that doing so is unavoidable [16]. Since his lecture in the field of nanotechnology, it subsequently given birth to nanomedicine. Nanomedicine is at the crossroads of chemistry, biology, engineering, material science, and clinical medicine and can be defined as the application of nanotechnology specifically to health care [17, 18]. More specifically, the two areas within nanomedicine that is focused on are how applications can be used

to develop and improve already existing systems of therapeutic and diagnostic treatments. The specificities of these two systems are as following: The diagnostic treatments are more aimed at diagnosing ailments within patients, the distinction from modern diagnostic tools is by utilizing nanotechnology, a strategy that has been implemented is implant imaging agents into nanoparticles where the goal is to have diagnosing abilities that allow for earlier detection of disease [18]. Two methods that have been employed is use of fluorescent nanomaterials for and magnetic nanoparticles for bioimaging. Fluorescent nanomaterials, especially for the monitoring and marking of cells and tissues, have become instrumental in the early detection of cancer and are as prevalent as magnetic resonance imaging (MRI) [19]. Several nanomaterials have been developed and synthesized for the function of acting as contrast agents during MRI. As the powerful magnet is focused on a person's body, the body reacts like water under a magnetic field. As the protons are aligned in accordance with the magnetic field, a radio wave frequency (RWF) is added to the magnetic field. Once the RWF is turned off, a signal is discharged which causes the MRI [20]. Functionally if the contrast agents, given to patients undergoing MRI, can cause the protons of the body to realign faster after the RWF is turned off, then the image given off by the signal will be of better quality allowing more accurate and timely diagnoses of diseases [21–24].

1.3 Role of Nanogels in Medicine

With the continual search of better diagnostic agents and techniques and more efficient methods of therapeutic treatment, the field of theranostics was birthed in the effort of combining therapeutic treatment of cancer with the ever improving diagnostic capabilities [18]. Theranostic nanomedicine has greatly improved the efficacy of chemotherapy against diseases like cancer. However, one of the major problems encountered with theranostics carrier is while creating nanoparticles for theranostics purposes does allow to have molecules that are size inappropriate to travel through the blood–brain barrier (BBB), the therapeutic loading agents are often in doses too small to provide proper treatment for ailments [25, 26]. A platform that would allow for the bypass of the BBB while still providing sufficient therapeutic agents is a nanogel. A nanogel by definition is a multipurposed physically or chemically crosslinked nanoscale polymeric network that is composed of hydrophilic and or hydrophobic moieties [25, 27–29]. The formation of a nanogel is parallel to that of a hydrogel in that it is a three-dimensional structure that is either physically or chemically crosslinked and able to contain a significant amount of water [30–33]. Nanogels comprise of smart stimuli responsive linkages such as pH, temperature, and reduction potential sensitive units which can ensure the site specific delivery of the loaded therapeutic components. One recent

example for such nanogel was reported by Ghorbani based on a Glutathione responsive nanogel that has potential use in a drug delivery system with the application as a diagnostic anti cancer drug. More specifically, precipitation polymerization of carbon dots (CD) and cationic dimethylamino ethyl methacrylate (DMAEMA) was used to prepare the nanogel [34]. Another recently published instance of the synthesis of a nanogel would be the synthesis of a silica nanoparticle nanogel as reported by Zhang [38]. This nanogel was synthesized as a drug-releasing nanoparticle, as a cancer diagnostic releasing agent of 5-aminolevulinic acid. Thus, it was clear that nanogels in general have advantageous properties such as high drug loading capabilities, load release kinetics are easily manipulated, and both hydrophobic and hydrophilic nanoparticles can be loaded inside of nanogels [35–37]. While traditional nanoparticles for theranostic purpose have shown advancement difficulties encountered therapeutically is lack of control over the kinetics of the drug release from therapeutic agents and the expiration of contrast agents being to rapid to give good resolution for MRI nanogels have been making progress in improving both problems [38–41]. In the current chapter, we are exclusively focusing on nanogels with multifunctional characteristics such as magnetic and fluorescent characteristics. These multifunctional nanogels could have a huge impact on the rapidly growing area of nanomedicine. Hence, it is essential to have an overview about the recent developments taking place in this area.

2 Magnetic Nanogels in Nanomedicine

2.1 Introduction to Magnetism: Fields and Faraday

Since antiquity, it has been known that a certain mineral, loadstone possesses the property of attracting iron objects. At various points, seafaring communities have exploited this property to navigate as a suspended loadstone will align north to south with the earth. Today we described this phenomenon as magnetism. Magnets and magnetism have been well explored in everything from compass needles and electric motors to magnetic resonance imaging devices and the large hadron collider at CERN. The formal description of magnetism began in the early nineteenth century with the work of Michael Faraday. Faraday coined the terminology “lines of force” to describe the mechanism of magnetism. Although his background in mathematics was weak, Faraday possessed a strong intuition and was able to study and exploit magnetic effects.

His famous “Faraday motor” was the first reported instance of an electric motor. Later with the insight and expertise of Maxwell, the description of magnetic fields was formalized and unified with the description of electric fields. This resulted in the famous set of Maxwell’s equations which form the basic framework of classical electrodynamics.

In the modern era since the advent of quantum mechanics, there has been much improvement in terms of accuracy and unification with other theories with respect to electromagnetism. Quantum electrodynamics mathematically describes the interactions of matter/light and harmoniously incorporates quantum mechanics and general relativity to describe the electromagnetic interaction. Taken together this framework forms one part of the Standard Model which attempts to describe all the fundamental interactions of matter and the fundamental forces, although gravity has yet to be harmonized. Despite this, the Standard Model predicts with great accuracy the electromagnetic phenomena and offers our best explanation of magnetic properties to date.

2.2 Role of Magnetism in Imaging

Magnetic resonance imaging (MRI) is characterized as a widely employed non-invasive technique for imaging in vivo for the diagnosis of various pathologies. The basic principle of MRI is that of proton relaxation in a strong magnetic field. The technique of MRI bears a striking resemblance to nuclear magnetic resonance (NMR) used in materials science and chemistry to elucidate chemical structure. In fact MRI was commonly referred to as "nuclear magnetic resonance imaging" or NMRI but the "nuclear" term was abandoned due to the negative connotations (nuclear weapons, radiation, Cold War, etc.). However, both techniques are essentially the same in principle. NMR was first described in the 1930s by experiments which were extensions of the famous Stern–Gerlach experiment. Atomic nuclear particles possess a quantity called spin associated with their intrinsic angular momentum. Thus, some nuclei will have an overall spin which is associated with an overall magnetic moment; however, some nuclei have a total spin equal to zero which results in no net magnetic moment (since spin values can take on positive or negative values). Taking protons (hydrogen nuclei) as an example they have spin values $m = \pm ½$. When subject to a strong magnetic field protons will align their spin accordingly. If a radiofrequency pulse were to disturb this alignment (due to an oscillating magnetic and electric field), then a resonance can be observed as the system tries to achieve equilibrium. The chemical environment can influence the characteristics of the resonance and, thus, chemical information can be measured. By advancing this technique further where the chemical information is mapped in three dimensions, then we arrived at MRI. MRI is, thus, NMR measurements mapped in 3D to form an image based on the chemical differences of the various parts of the subject being measured. MRI gained traction as a diagnostic technique in the 1970s and 1980s and remains vastly important in the suite of modern medical imaging techniques.

There are two main types of MRI imaging based on the mode of relaxation. T1 imaging mode is based on the spin–lattice relaxations where the magnetization is in line with the static field. T2 imaging mode is based on spin–spin relaxation and is characterized by magnetization which is transverse to the static field.

2.3 MRI and Nanoparticles Research

An important consideration of any imaging technique is the ability to achieve and measure differences in contrast. MRI is no different, and one of the most common contrast agents is the gadolinium (III) ion which is typically available as chelated product which is both water soluble and sequesters the Gd (III) ion. Other elements may serve as contrast agents and form the basis of a subset of nanoparticles (NP) research. NP contrast agents were described in the literature as early as the 1980s as MRI was gaining popularity. One important early communication in 1986 by Dias and Lauterbur showed the efficacy of iron nanoparticles, specifically magnetite, as contrast agents in canine models [42]. However, the particles being on the order of 0.05 μm showed a propensity to accumulate in the certain organs, namely the liver and spleen. This represents an early recognition of a limiting factor concerning nanoparticles which is the accumulation at specific non-target organs. With the case of iron-based NPs, iron toxicity is a concern. As a result, groups began to see the value of encapsulation of iron NPs to mitigate this effect. In 1989, Pouliquen and colleagues applied the methodology of encapsulation for targeting liver delivery [43]. The results indicated ninefold increase in liver uptake as a result.

This trend of investigation continued for the next decades with iron-based systems as a popular choice for NPs. By the early 1990s, the field of iron-based NP systems was very well established and there are examples of work to try to tune the pharmacokinetics. Notably, Pouliquen and colleagues reported in 1991 a study in murine models of superparamagnetic iron-NPs for determining the metabolism and distribution [44]. The authors concluded that the structure/property relationship correlates with the biodistribution and degradation kinetics. By the mid-1990s, additional imaging applications began to emerge. One example is that of tumor imaging. In 1996, Tiefenauer and colleagues modified magnetite NPs with artificial polypeptides with the aim to target tumors for imaging [45]. NPs were further modified with various biomolecules to aid in retention time. The murine model with grafted tumors demonstrated limited success with one specific peptide but demonstrated the concept. Going against the trend of coatings, Babes and colleagues in 1999 reported a method for producing uncoated and stable iron-NPs [46]. However, ironically they reported preparing for animal studies by coating with polymers.

In the last two decades, the literature has surged with large numbers of additional papers describing both metallic and non-metallic systems. Various additional functions were being explored. For example, iron-NP systems as drug delivery agents with imaging capabilities were reported by Chertok and colleagues in 2008 [47]. A 2009 review of NP systems by Na and colleagues summarized a variety of inorganic systems for MRI contrast capability [48]. The utilization also expanded to include additional imaging techniques. A combination of functions including MRI,

positron emission tomography (PET), and near-infrared fluorescence (NIRF) was reported by Xie and colleagues for theranostic purposes which utilized iron-NPs [49]. Additionally, some interesting new systems were being developed. A notable example is lipid-based NP systems which were reviewed by Mulder and colleagues in 2006 [50].

One interesting aspect of MRI NP research is the ability to produce heat on demand or targeted hyperthermia. In 2008, Hadjipanayis and colleagues reported an iron-based NP system with improved magnetic properties that they put forth as the beginning of the new generation of iron-NP systems for targeted hyperthermia applications [51]. In 2009, Jang and colleagues reported an improvement in MRI contrast and hyperthermia-inducing properties of magnetic NP by introducing dopants, namely zinc, into their system [52]. Barick and colleagues reported carboxyl functionalized iron-NP system toward the development of enhanced water stability and biocompatibility in 2014 [53]. A review by Hilger and Kaiser in 2012 and another review in 2016 by Bianco-Andujar and colleagues show that this area of research is still quite active of wide interest toward MRI theranostics [54, 55]. Recent reports indicate the trends that dominate the current literature including multimode MRI. For example, Sanchez-Cabezas and colleagues reported a dual T1/T2 imaging capability combined with magnetic hyperthermia for, what they termed, ultrasmall superparamagnetic iron-NPs [56]. The fields will likely exhibit steady growth as the need for theranostic devices and techniques continues.

2.4 *Role of Nanogels with Magnetic Characteristics for Nanomedicine*

Nanogels endowed with magnetic properties are one of the main candidates used for bioimaging applications. The higher encapsulation efficiency of the magnetic component inside the core of the nanogel makes it an ideal carrier for magnetic nanoparticles. MRI-guided therapies toward diseases like cancer is an emerging area in nanomedicine; in this context, nanogel plays a crucial role in the safe and efficient delivery of the contrast agent in the disease area. Magnetic nanoparticles such as iron oxide and gadolinium can be efficiently loaded inside the nanogel to construct a multifunctional nanoplatform. Nanogels can also respond to different stimuli such as pH, temperature and redox potential. This property makes it more favorable for fabricating smart magnetic theranostic nanocarriers. There are many reports on the development of magnetic nanogels for biomedical applications. The table below gives a brief overview of the different reports on magnetic nanogels.

Reference No	Magnetic component	Polymer component	Application
[57]	poly-[N (2,2difluoroethyl) acrylamide]	poly[N-(2-hydroxypropyl)-methacrylamide]	MR imaging
[58]	Gadolinium(III)	Hyaluronic acid	MR imaging of cancer
[59]	Gadolinium(III)	Poly(N-vinylcaprolactam)	MR imaging of cancer
[60]	Iron oxide nanoparticles	Cholesterol-bearing pullulan	Magnetically guided protein transduction
[61]	Iron oxide nanoparticles	Transferrin functionalized polyethylene glycols	Magnetic devices for circulating tumor cells
[62]	Iron oxide nanoparticles	Glycol chitosan	MR imaging of cancer
[63]	Iron oxide nanoparticles	Hyaluronic acid	MR imaging and drug delivery
[64]	Iron oxide nanoparticles	Sodium alginate	Sorption of heavy metal ions
[65]	Iron oxide nanoparticles	Poly (N-isopropylacrylamide-co-acrylic acid)	MR imaging of cancer
[66]	Gadolinium(III)	Polyethyleneimines	MR imaging of cancer
[67]	Iron oxide nanoparticles	2-vinylpyridine and divinylbenzene	Gene delivery
[68]	Iron oxide nanoparticles	Polycarboxybetaine methacrylate	MR imaging and drug delivery
[69]	Iron oxide nanoparticles	Polyvinyl pyridine	Drug delivery
[70]	Iron oxide nanoparticles	*N*-(2-aminoethyl) methacrylamide hydrochloride	MR imaging

There are some very interesting studies reported on the development of magnetic nanogels for different applications. One thing is clear that a special emphasis is always given to magnetic nanogels in the area of theranostics. Recently, Addisu et al. have reported a manganese-chelated alginate–polydopamine nanogels for T1-based magnetic resonance imaging [71]. The designed nanogel was based on alginate–dopamine and cations Mn/Ca. The ionic interactions between the carboxylic acids of the alginate with the respective cations were found to impart stability to the formed magnetic nanogel (Fig. 3). The prepared nanogel has shown strong paramagnetic properties with good T1-weighted MRI imaging capability on cancer cells both in vitro and in vivo. The nanogel was demonstrating imaging potential having good signal to ratio with longer tumor and anatomical imaging.

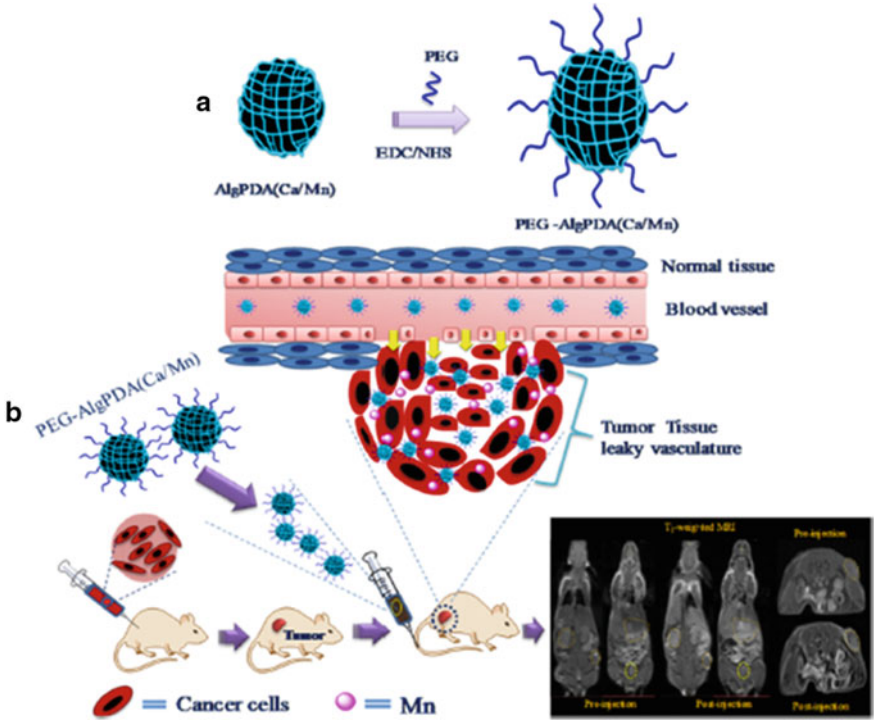

Fig. 3 **a** Process of preparing PEG–AlgPDA(Ca/Mn) NG and **b** passive tumor targeting of PEG–AlgPDA(Ca/Mn) NG through the defective tumor microvasculature pH is used to trigger local Mn ion release from the MRI CAs in the tumor. "Adapted with permission from [71]. Copyright (2018) American Chemical Society"

In another study, cortez et al. reported a hybrid nanogel which is formed by the combination of thermoresponsive polymer oligo (ethylene glycol) methyl ether methacrylate and superparamagnetic iron oxide nanoparticles [72]. Doxorubicin was loaded inside the core of the nanogels to test its therapeutic efficacy. It was found that the nanogel was exhibiting both temperature and magnetic field responsive drug release characteristics (Fig. 4). More specifically, the nanogel was exhibiting a swelling–deswelling behavior at 46 °C, and magnetic field-assisted heat generation (hyperthermia) was also accelerating the drug release kinetics. Hence, the designed nanogel clearly exhibited great control in tailoring the therapeutic responses against cancer.

Recently, Caro et al. have reported a manganese-based nanogel for pH responsive dual-mode MRI imaging (T1- and T2-weighted MRI) [73]. The designed nanogel was based on a copolymer of 4, vinylpyridine and divinylbenzene which was further chelated with manganese to form the magnetic hybrid nanogel (Fig. 5).

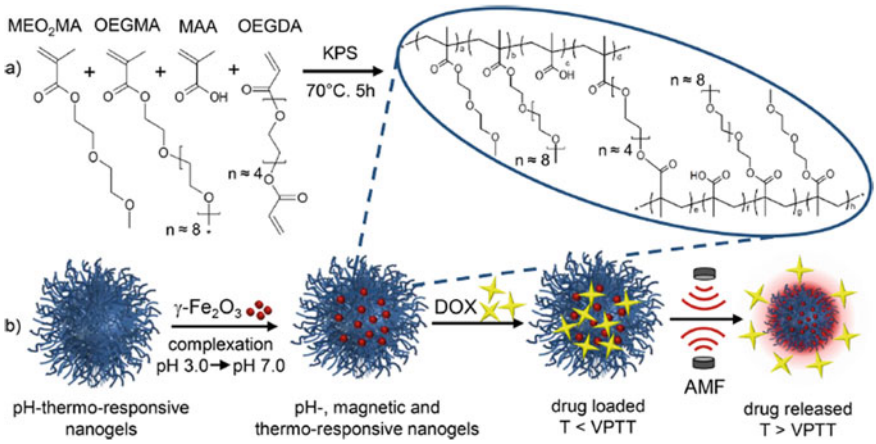

Fig. 4 Illustration of MagNanoGel synthesis and remotely controlled drug delivery under an AMF: **a** conventional aqueous precipitation radical copolymerization reaction of nanogels based on oligo(ethylene glycol) methyl ether methacrylate monomers, **b** schematic illustration of the MagNanoGel synthesis, loading, and release of DOX under an AMF. "Adapted with permission from [72]. Copyright (2017) American Chemical Society"

The nanogel exhibits pH responsive swelling behavior via the protonation of the pyridine units of the nanogel which may change the hydration state of the nanogel making it swelled at low pH. This process facilitates the entry of more water inside the nanogel matrix which will in turn affect the T1 and T2 relaxation time of the protons. This is the working principle of this nanogel-based pH switch. However, the swelling behavior of the nanogel should be tuned in the pH range of 6.3–7 (which is almost the same condition in cancer cells) to make it more applicable for tumor imaging.

Even though the many of the reported magnetic nanogels exhibits good tumor imaging potential, they still face from some major drawbacks such as rapid clearance from the body, poor signal-to-noise ratio, and repeated administration. These features limit the translational potential of magnetic nanogels in nanomedicine. In a study, Chan et al. have attempted to address these issues by developing a gadolinium-chelated pullulan nanogels [74]. Cholesterol and acryloyl were used to modify the surface of the pullulan polymer, and further these two different modified pullulan polysaccharides were photo cross-linked in the presence of gadolinium to prepare the magnetic nanogel (Fig. 6). The designed nanogel was found to have longer residence time and better signal-to-noise ratio during tumor imaging. More specifically, this magnetic nanogel demonstrated high signal enhancement for 7 days on 4T1 tumors in mice. Hence, it was clear that the reported magnetic nanogels have greatly improved the functional performance especially toward tumor imaging applications.

Recently, there is a great interest on the development of multifunctional magnetic nanogels which can integrate more than one imaging modality in a

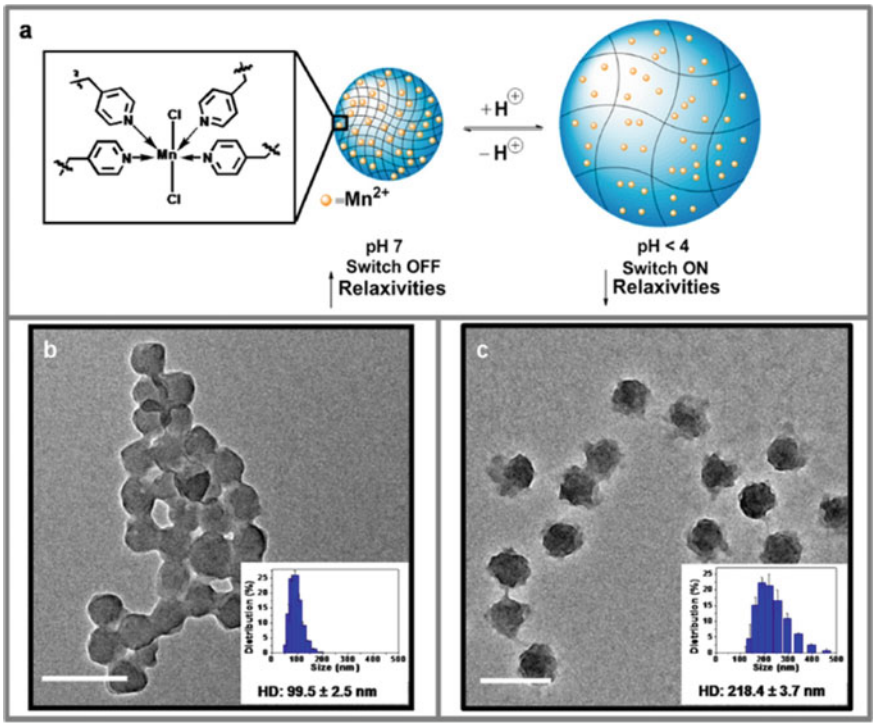

Fig. 5 **a** Scheme of the swelling process of the nanogel, where a decrease in pH promotes an increase in the hydrodynamic size. **b** TEM images of Mn chelate NGs at pH 7 and **c** TEM images of the swollen Mn chelate NGs at pH 3. The scale bar is 200 nm in both images. Insets in (**b**) and **c** show histograms of the hydrodynamic diameter (HD) size distributions. "Adapted with permission from [73]. Copyright (2017) American Chemical Society"

single-nanoparticle framework. It was anticipated that these nanogels with multi-imaging potential will give a detailed information regarding the pathophysiology of diseases like cancer. In this regard, Wang et al. have reported a nanogel with dual imaging potential (magnetic and ultrasound) [75].

The designed nanogel was based on a polysaccharide cationic polymer glycol chitosan nanogel which was functionalized with superparamagnetic iron oxide nanoparticles (Fig. 7). Detection of reactive oxygen species (ROS) such as hydrogen peroxide (H_2O_2) and superoxide anion ($O2^-$) will provide more insight on the pathophysiological information of diseases like cancer. In this regard, the designed dual-imaging nanogel was loaded with dual ROS responsive enzymes catalase and superoxide dismutase. This smart enzyme responsive nanogel was able to generate sufficient amount of oxygen bubbles for ultrasound imaging. Furthermore, the nanogel was also able to preferentially accumulate on the acidic environment of the targeted area which allows generating strong magnetic resonance imaging from tumor regions. Results have shown sevenfold increase in the

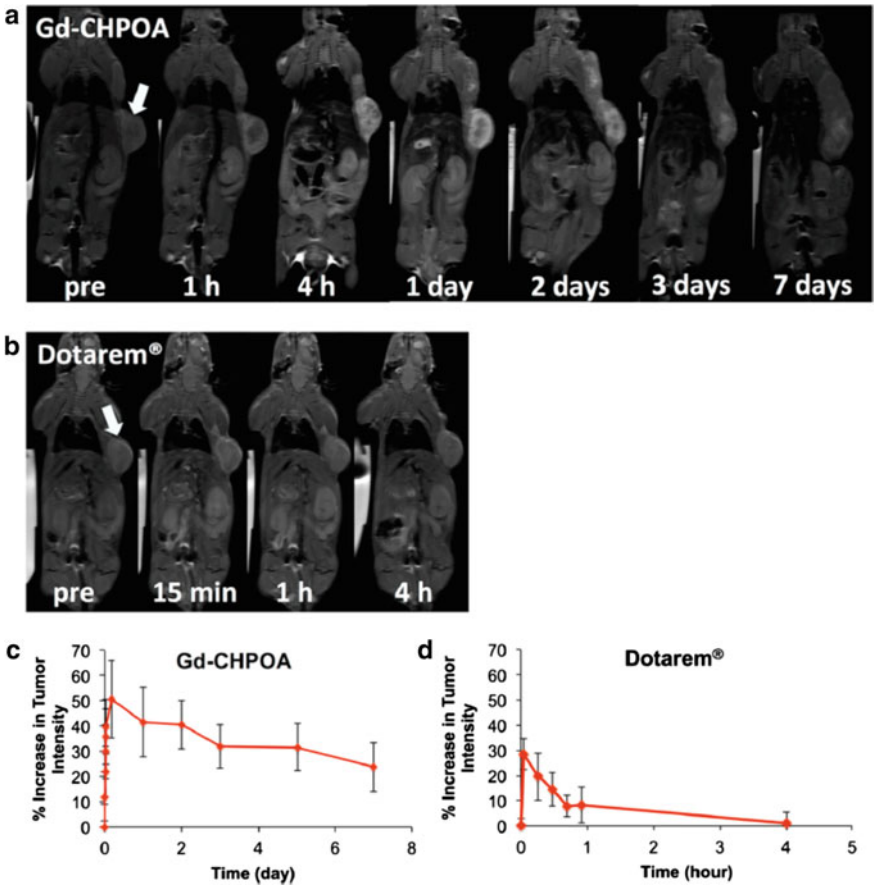

Fig. 6 Gd-CHPOA nanogels delineate 4T1 tumor grafts. MRIs of 4T1 tumor-bearing mice injected with **a** Gd-CHPOA ([Gd] = 0.1 mmol/kg) or with **b** Dotarem at various time points. Regions of interest (tumors) are indicated by white arrows. Signal enhancement in tumor from **c** Gd-CHPOA or d Dotarem over time. "Adapted with permission from [74]. Copyright (2017) American Chemical Society"

signals from tumor. These results have suggested the excellent future potential of the nanogel to explore more insight about the real-time pathophysiology of disease like cancer.

Drug release from the magnetic nanogels can be easily tuned or manipulated with the application of an external magnetic field. Also the heat generated during this process can be used to kill cancer cells (magnetic hyperthermia). Due to the mentioned benefits, a magnetic nanogel plays a crucial role in theranostic nanomedicine. In this regard, an interesting study was reported by Chiang et al. has reported the development of a hollow theranostic magnetic nanogel for simultaneous MRI imaging and cancer therapeutics [76]. The designed nanogel was

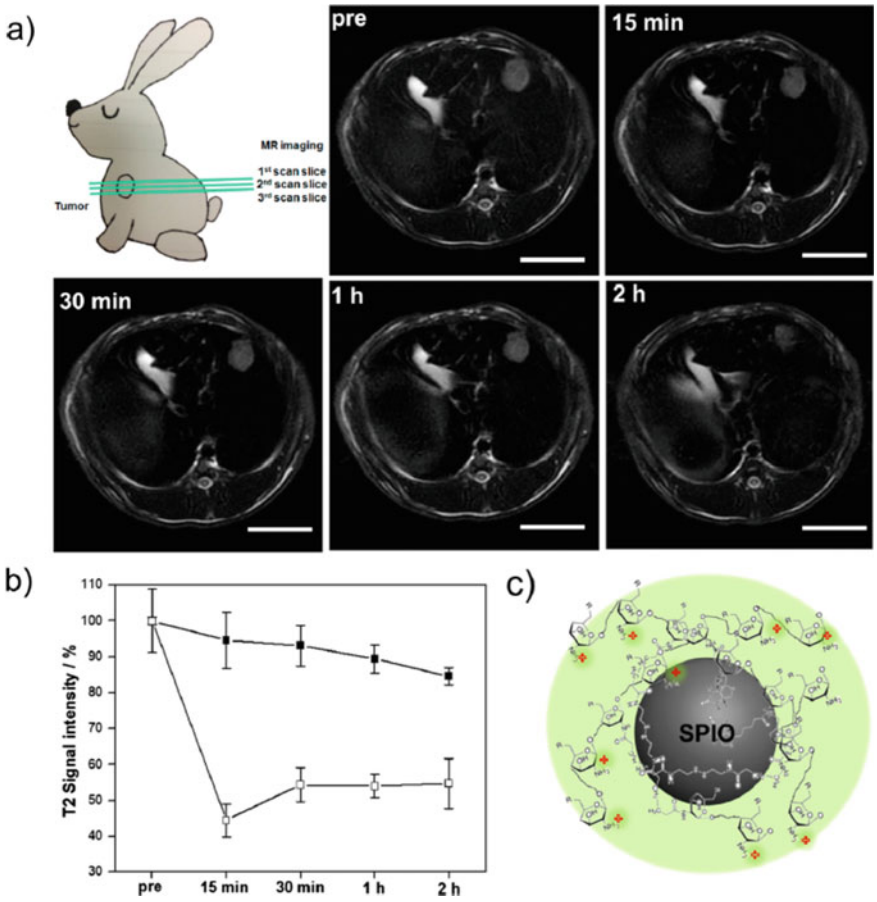

Fig. 7 In vivo T2-weighted MR imaging. **a** T2-weighted MR images and **b** their corresponding signal intensities for rabbits bearing VX2 tumors on the livers preinjection and 15 min, 30 min, 1 h, and 2 h after intravenous SGC injection. **c** schematic mechanism of enhanced MR imaging. "Adapted with permission from [75]. Copyright (2015) American Chemical Society"

prepared from the co-assembly of superparamagnetic iron oxide nanoparticles with a graft copolymer (polyethylene glycol and poly-N-Isopropylacrylamide) (Fig. 8). The hollow nanogel exhibited a high SPION loading capability of 44 wt%. The pH responsive gel layer of the nanogel confers it the capability of pH responsive magnetic resonance imaging. More specifically, when the pH was tuned from 4 to 7.4, the transverse relaxivity (r_2) of the nanogel increased from 138.5 to 265.5 $mM^{-1}S^{-1}$. An external magnetic field can direct this hollow nanogel toward the region of interest, also the drug loaded inside the nanogel can be triggered with the help of magnetic field. This greatly improves the therapeutic response of the nanogel.

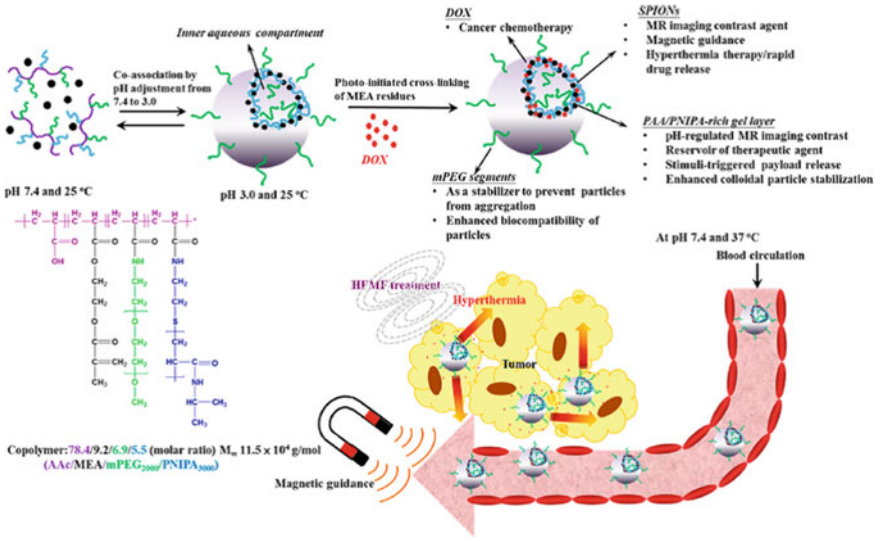

Fig. 8 Development of the DOX-loaded hollow hybrid nanogels serving as a multifunctional anticancer theranostic platform. "Adapted with permission from [76]. Copyright (2013) American Chemical Society"

3 Role of Fluorescence Imaging in Nanomedicine

Fluorescence bioimaging is one of the widely accepted imaging modalities used for disease diagnostics. The high sensitivity and facile instrumentations make them an attractive along with other imaging modalities such as ultrasound and magnetic resonance imaging. Many different properties of fluorophores such as its photostability, quantum yield and fluorescence lifetime will decide the functional performance of any fluorophores for bioimaging [77–80]. Some of the major drawbacks faced by the fluorophores are lack of tissue penetration, tissue autofluorescence, absorption by proteins and water molecules present in the body [81–83]. These issues could be addressed by the emergence of fluorophores having the NIR region (650–900 nm) emission characteristics [84]. NIR light has the highest tissue penetration which could go to several centimeters without any significant overlap from the autofluorescence from the body [85]. Hence, always NIR fluorophores get special priority for fluorescence-based bioimaging applications. Therefore, fluorophores having biocompatibility and NIR emission characteristics could be ideal for bioimaging applications. NIR-emitting dyes such as indocyanine green, squaraine, semiconductor quantum dots and carbon dots and quantum dots are well explored for bioimaging applications [86–90]. Some of the properties of these NIR fluorophores such as photostability, quantum yield and fluorescence lifetime will decide the functional performance of them for bioimaging applications. Ideally, NIR fluorophores with higher photostability, quantum yield and

fluorescence life time in the order of nanoseconds or more will be ideal for bioimaging applications [91–94]. Apart from the above-mentioned material properties, biocompatibility is another important parameter which will govern the translational potential of these NIR fluorophores. Ideally, fluorophores should perform the imaging function without eliciting any toxicity issues for the normal cells and after performing its intended function, it should be degraded or eliminated from the body. Currently employed NIR fluorophores have its own merits and demerits. For instance, the quantum dots are endowed with very high quantum yield and photostability but they still face toxicity concerns [95–97]. In the case of organic dyes, they do not have serious toxicity concerns but they have problems with photostability [98–100]. Hence, it was clear that a good integration of functional performance with biocompatibility could be a crucial factor for determining the translational potential of these fluorophores for biomedical applications.

3.1 Role of Nanogels with Fluorescent Characteristics in Nanomedicine

Nanogels play a crucial role in nanomedicine by performing highly efficient and safe imaging. The higher water content present in the nanogel confers it with excellent loading or conjugation of the fluorescence moieties [101–103]. The fluorescence property can be imparted to the nanogel by adding fluorescent moieties such as organic dyes, quantum dots, and carbon dots. These fluorescent nanogels can perform simultaneous therapeutic and diagnostic functions. Even though they have good functional performance, they have concerns regarding the biocompatibility especially for fluorescent moieties such as quantum dots [104]. Hence, there is a great interest in developing intrinsically fluorescent nanogels which does not require any external imaging agents. The intrinsically fluorescent nanogels can there for avoid any external fluorescent moieties which will in turn improve the overall safety of the nanogels for in vivo applications.

Recently, Men et al. have reported a fluorescent nanogel based on zwitterionic poly-(sulfobetaine methacrylate) [105]. The nanogel was composed reduction sensitive disulfide bonds which confer it with reduction sensitive drug release profile and capability to conjugate fluorescent moieties (Fig. 9). Fluorescent dye Cy 7.5 maleimide was further conjugated with the reduction sensitive disulfide linkages. Doxorubicin was loaded inside the fluorescent nanogels to assess its therapeutic performance. It was found that the nanogels release only 7% of the loaded drug in physiological conditions but in reduction environment (10 mM glutathione), 85% of the drug was released. This result has clearly revealed the reduction sensitive drug release profile of the nanogel. Also, the fluorescence imaging in a mice model has revealed favorable characteristics for tumor treatment such as higher tumor accumulation, longer circulation lifetime and reduction-sensitive release of the drug in tumor region.

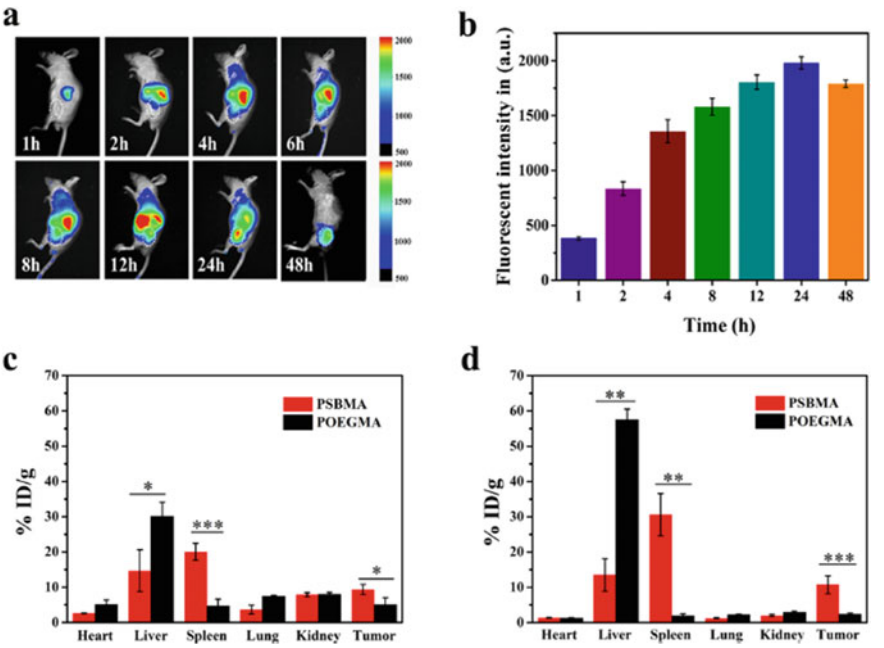

Fig. 9 Tumor targeting delivery of PSBMA nanogels. **a** Representative NIFR imaging of FaDu tumor-bearing nude mice at different timepoints post-injection with PSBMA-Cy7.5 nanogels (200 μg/mL, 100 μL). White dotted ellipses indicated tumors. **b** Fluorescent intensity in tumors on the basis of NIFR images. Biodistribution of POEGMA and PSBMA nanogels in FaDu tumor-bearing mice at 24 h (**c**) and 48 h (**d**) post-nanogel injection. "Adapted with permission from [105]. Copyright (2018) American Chemical Society"

In a different study, Chambre et al. have reported a fluorescent multifunctional nanogel which can perform targeted drug delivery and imaging [103]. The nanogel prepared was based on polyethylene glycol and maleimide which was further crosslinked with dithiols (Fig. 10). The PEG grafts present in the nanogel confers it with thermoresponsive characteristics. The maleimide and residual thiol units present in the nanogel were further utilized for conjugating fluorescent indocyanine cy5 dye and a cancer cell targeting peptide.

Results have suggested the good targeting potential of the prepared nanogels on MDA-MB-231 breast cancer cells. Doxorubicin was loaded inside the nanogels to assess its therapeutic performance against the breast cancer cell lines. It was found that the nanogels without any targeting peptide were exhibiting lesser therapeutic response toward the cancer cells in comparison with the targeted nanogels. Taken together these results suggested the multifunctional nature of the prepared nanogel toward cancer therapy.

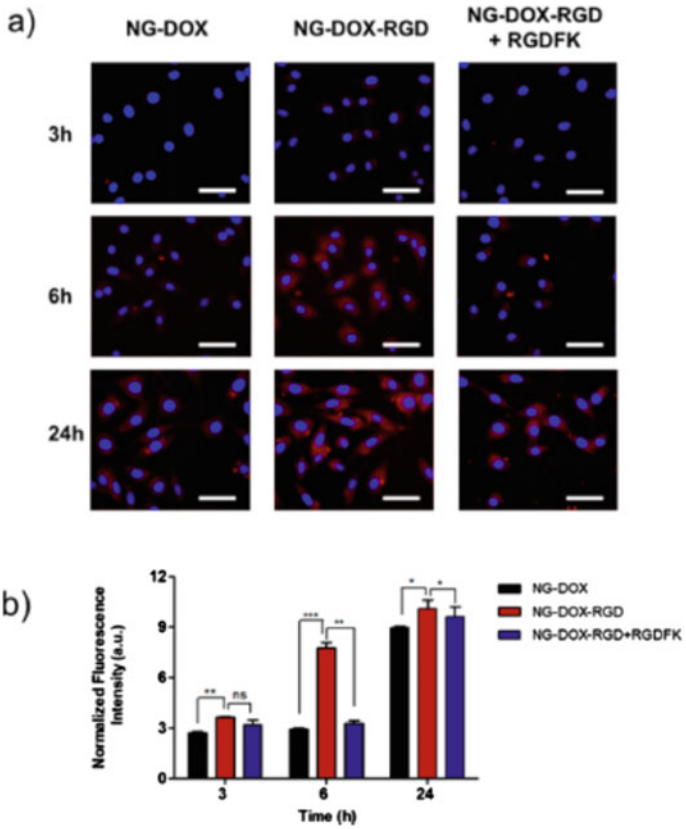

Fig. 10 Merged fluorescence images of MDA-MB-231 cells treated with nanogels with only doxorubicin (NG-DOX), nanogels conjugated with doxorubicin and cRGDfC (NG-DOX-RGD), and free cRGDfC and NG-DOX-RGD nanogels (NG-DOX-RGD+RGDFK). Cells were incubated at 37 °C for different time periods (3, 6, and 24 h). The scale bar is 100 μm. **b** Normalized fluorescence intensity for NG-DOX, NG-DOX-RGD, and NG-DOX-RGD+RGDFK at 3, 6, and 24 h. "Adapted with permission from [103]. Copyright (2018) American Chemical Society"

Toxicity is the major concern which limits the translational potential of imaging agents. Carbon dots are found to be a biocompatible fluorophores when compared to the inorganic quantum dots for imaging applications. Hence, nanogels loaded with carbon dots have good importance in the area of nanomedicine. In this regard, wang et al. have reported a nanogel comprising of chitosan and carbon dots [106]. This hybrid nanogel was found to integrate near-infrared (NIR) imaging and NIR/pH responsive drug release characteristics (Fig. 11). The chitosan units of the nanogel endow it with high drug loading potential, meanwhile the carbon dot units gives it bright fluorescence and NIR photo thermal conversion. It has also exhibited good colloidal stability with brighter UV-NIR fluorescence emission characteristics. Smarter or on demand drug release can be accomplished using this nanogel via

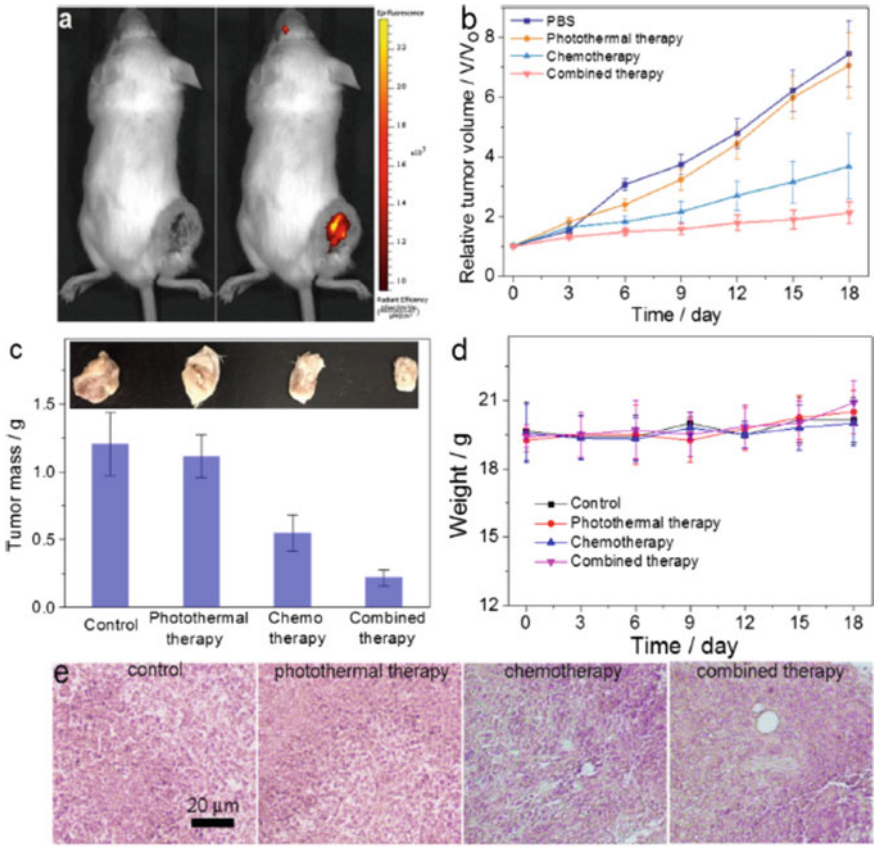

Fig. 11 In vivo tumor therapy of DOX-loaded CCHNs. **a** NIR image of the tumor site from a mouse intravenously treated with DOX-loaded CCHNs at day 18 post-treatment. **b** Tumor growth curves of mice after receiving different treatments including control, photothermal therapy, chemotherapy, and combined photothermal–chemo therapy. **c** Mass and pictures of tumors obtained from mice on day 18 after receiving different treatments. **d** Monitoring curves of the body weight of mice over the whole treatment period. **e** H&E-stained sections of tumors obtained from mice after different treatments including control, photothermal therapy, chemotherapy, and combined therapy. "Adapted with permission from [106]. Copyright (2017) American Chemical Society"

stimuli such as NIR and pH. In vivo experiments on tumor bearing mice have revealed that this nanogel can easily permeate into the tumor site and give high therapeutic response. The chemo and photothermal treatments were successfully demonstrated on tumor-bearing mice. It was found that the maximum therapeutic outcome was generated by the NIR photothermal treatments of the tumor site using the carbon dot-embedded nanogels. Taken together, these results suggest the good theranostic potential of the prepared nanogel for cancer.

All of the above-discussed fluorescent nanogels need external fluorescent moieties such as fluorescent dyes, carbon dots and quantum dots to accomplish imaging. But nevertheless, there are still some major questions are existing such as the stability of the conjugated fluorescent moieties inside the body and possible toxicity concerns raised by these fluorescent labels. These issues have to be addressed in order for the successful translation of these fluorescent nanogels from laboratory to clinics. In this regard, nanogels with intrinsic fluorescent characters receive a special attention in nanomedicine. In an interesting study by Li et al. reports the development of an intrinsically fluorescent redox-sensitive hyaluronic acid nanogel for breast cancer therapy [107]. This intrinsically fluorescent nanogel was prepared by combining nanoprecipitation and catalyst-free photo crosslinking of hyaluronic acid-co-oligo (ethylene glycol) tetrazole with L-cystine dimethacrylamide. Cytochrome C was loaded as a model protein inside the core of this nanogel, and it exhibited a good loading efficiency around 40.6 wt% (Fig. 12). The prepared nanogel exhibited intrinsic fluorescence emission at 510 nm. The reduction-sensitive disulfide linkages present on the back bone of the nanogel conferred it with a reduction-sensitive release profile of the loaded protein. The result with the breast tumor xenograft has revealed that the prepared nanogel can effectively suppress the growth of the tumor with low systemic side effects. The intrinsic fluorescence characteristics of this nanogel can be exploited for tracking the tumor penetration of the nanoparticles in vivo. These results suggest the good future potential of this nanogel as a smart protein delivery platform in nanomedicine.

However, the major drawback of this nanogel is the chances of interference of autofluorescence form the body, since the emission of the nanogel lies in the visible region. Hence, it is more appropriate to develop an intrinsically fluorescent smart nanogel with near IR emission characteristics which can overcome the autofluorescence issued from the body. In this regard, Vijayan et al. have reported a stimuli responsive nanogel with intrinsic fluorescence at near IR [108]. The prepared nanogel was prepared from a fluorescent copolymer of polypropylene fumarate. PEG, citric acid and glycine (Fig. 13). This copolymer was further crosslinked with a pH responsive N,N dimetheylethyl methacrylate to form a pH responsive self-fluorescent nanogel. The prepared nanogel was found to exhibit excitation wavelength-dependent fluorescence emission characteristics which range from visible to near IR.

Doxorubicin was loaded as a model drug inside the nanogel, and it was found to have high drug loading efficiency of 80%. The nanogel also demonstrated a pH responsive release behavior of the loaded drug demonstrating the pH responsive drug release profile. The in vivo imaging of the nanogel in mice model has clearly demonstrated the near IR imaging potential of the nanogel. Also, the biodistribution studies have revealed that the nanogel will be excreted from the mice body after 48 h.

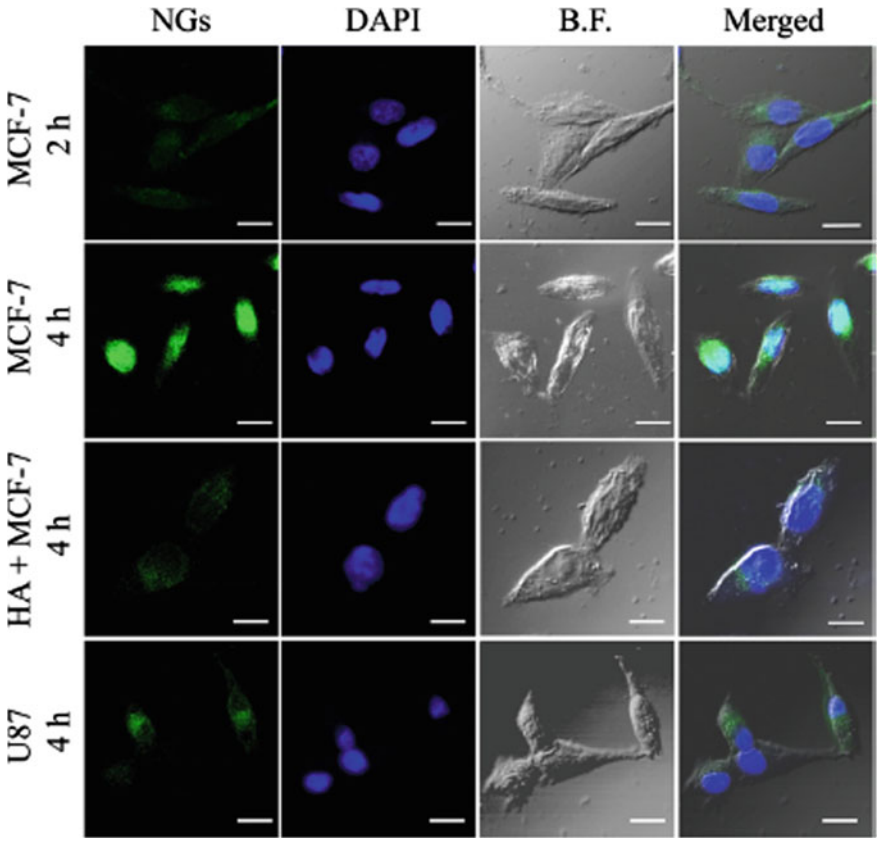

Fig. 12 CLSM images of MCF-7 and U87 cancer cells after incubation with 0.8 mg/mL blank HA-NGs "Adapted with permission from [107]. Copyright (2016) American Chemical Society"

4 Magneto-Fluorescent Nanocarriers in Nanomedicine

Recently, multifunctional nanoparticles which are capable of combining different imaging modalities are gaining significant attention in nanomedicine [109–111]. The major reason for this observed trend is that these nanocarriers can combine synergistically multiple imaging modalities such as fluorescence and magnetic resonance imaging in a single-nanoparticle framework. A nanocarrier capable of combining both the magnetic and fluorescence capabilities together in a single domain is known as magneto-fluorescent nanocarriers. They have immense potential in the diagnostics and treatment of diseases like cancer. The accuracy and sensitivity of diagnosing different types and grades of cancer can be greatly improved with help of combining different imaging modalities in a single nanoparticles framework [112, 113]. The magnetic property is not only used for imaging perspectives, but also they are explored for performing some therapeutic

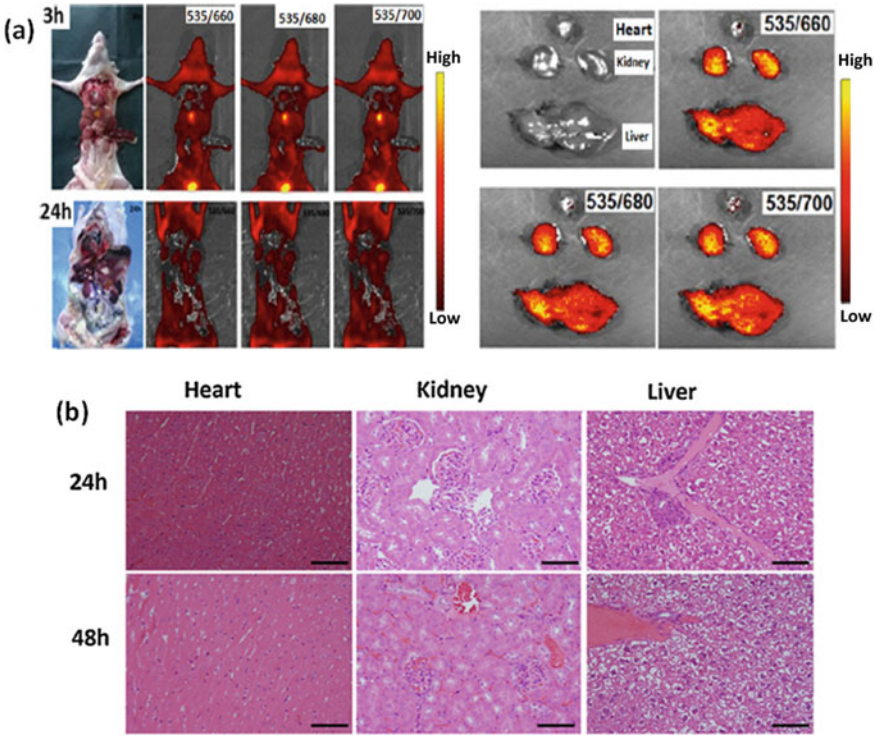

Fig. 13 Ex vivo imaging of organs of mice after 3 h and 24 h post-injection depicting biodistribution (**a**) (Inset shows the excitation and emission wavelengths detected with cutoff filters). H&E stained images of organs of mice at 24 h and 48 h post-injection (**b**). "Adapted with permission from [108]. Copyright (2016) Elsevier Publishers"

functions. This is mainly achieved by exploiting the heat generation capability of the magnetic nanoparticles in response to alternating magnetic field which in turn produces significant amount of heat to kill cancer cells; this phenomenon is termed as magnetic hyperthermia [114, 115]. Hence, a magneto-fluorescent nanocarrier can simultaneously perform the therapeutic and diagnostic (theranostic) functions in a single domain. The design of a magneto-fluorescent nanocarrier comprises of a magnetic nanoparticles core which is conjugated (physically or chemically) to a fluorophore. To increase the specificity of these nanocarriers toward diseases like cancer, usually they will be tethered with targeting agents like antibodies/peptides to ensure the site specific delivery of the nanocarriers. The picture below represents the design of a magneto-fluorescent nanocarrier (Fig. 14).

Alternatively, the magnetic field can be also employed for guiding the nanoparticles toward the region of interest. The most challenging aspect of fabricating a magneto-fluorescent nanocarrier is to preserve both the magnetic and fluorescent characteristics after the formation from their individual counterparts.

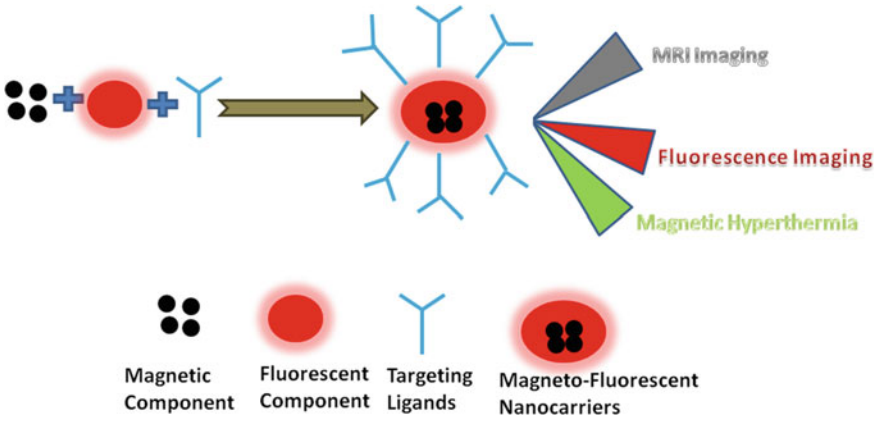

Fig. 14 Schematic representation of a magneto-fluorescent nanocarrier

Usually, fluorescence phenomenon can be quenched in the presence of a magnetic nanoparticle. Hence, careful design strategies are required to preserve both fluorescence and magnetic properties together in a single-nanoparticle framework. Recently, there are some reports focusing on the development of magneto-fluorescent nanocarriers.

4.1 Role of Magneto-Fluorescent Nanogels in Nanomedicine

Nanogels receive a special attention in nanomedicine to fabricate magneto-fluorescent nanocarriers. The different functional groups present on the surface of the nanogel can be easily conjugated with magnetic and fluorescent moieties to design magneto-fluorescent nanogels. They can efficiently perform theranostic functionalities in a single-nanoparticle framework. In an interesting study by Wu et al. reports a magneto-fluorescent core–shell hybrid nanogel [116].

The core–shell nanogel was fabricated by the growing a pH responsive gel shell of poly-(ethylene glycol-co-methacrylic acid) over nickel–silver bimetallic core nanoparticles (Fig. 15). The prepared nanogel was highly multifunctional since it can combine different functions such as pH dependent magnetic manipulation, fluorescent pH sensing, cell imaging, and drug delivery. The physico-chemical environment of the metallic silver core was highly dependent on the pH variations of the surroundings which may induce some volume phase transition of the gel layer. During this process, the metallic silver present inside the core of the nanogel can convert biochemical signals into optical signals which will give endow fluorescence property to the nanogels. The nanogel also exhibited pH-dependent magnetic properties. The in vitro cell studies revealed that this multifunctional nanogel can overcome cellular barriers and light up the mouse melanoma cells.

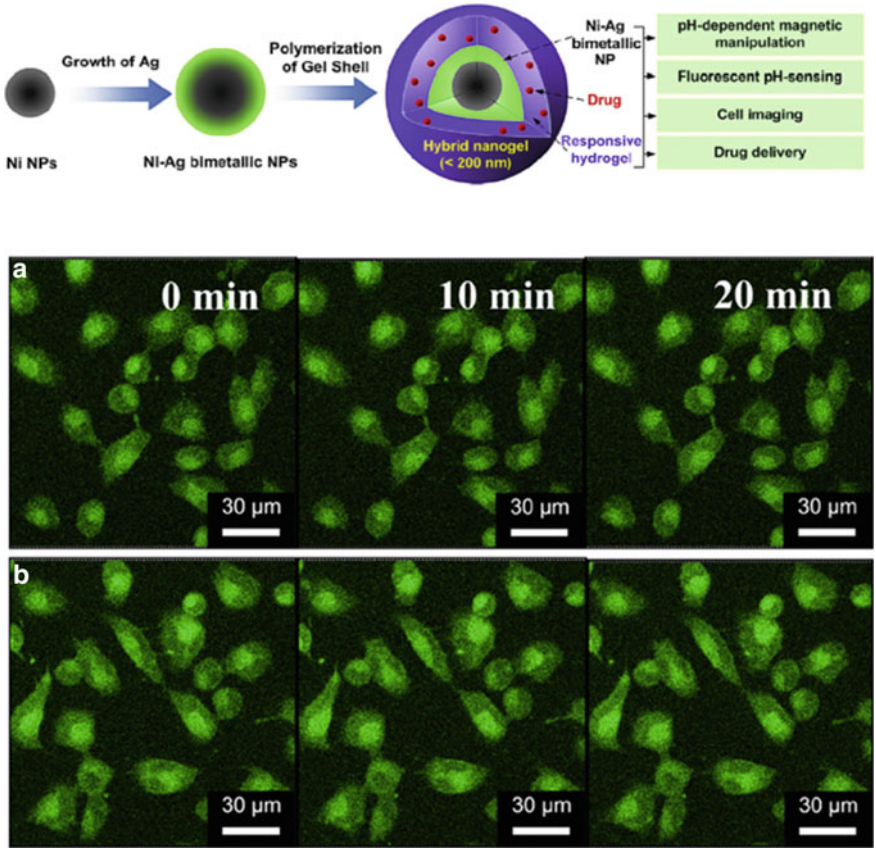

Fig. 15 Schematic illustration of the design of hybrid nanogel and scanning confocal images of B16F10 cells incubated with the Ni–Ag@p(EG-MAA) hybrid nanogels of **a** NAG-1 and **b** NAG-2, respectively. "Adapted with permission from [116]. Copyright (2011) Elsevier Publishers"

In another work, Shen et al. have reported a magneto-fluorescent nanogel based on chitosan, CdTe quantum dot and super paramagnetic iron oxide nanoparticles [117]. Folate-conjugated tertrapeptides were conjugated to the surface of this magneto-fluorescent nanogels to enable specificity (Fig. 16). Camptothecin was loaded as a model anticancer drug inside the core of the nanogel. The in vivo experiments have shown that this nanogel can be directed toward the tumor region by using an external magnetic field. The folate decorated nanogel has shown specific targeting to lung cancer A549 cells in vitro. The quantum dots present inside the nanogel can be utilized to track the internalization of the nanogel into cancer cells. Taken together, these results suggests the multifunctional characteristics of the prepared nanogel such as magnetic guidance, specific targeting toward tumor, and good therapeutic response.

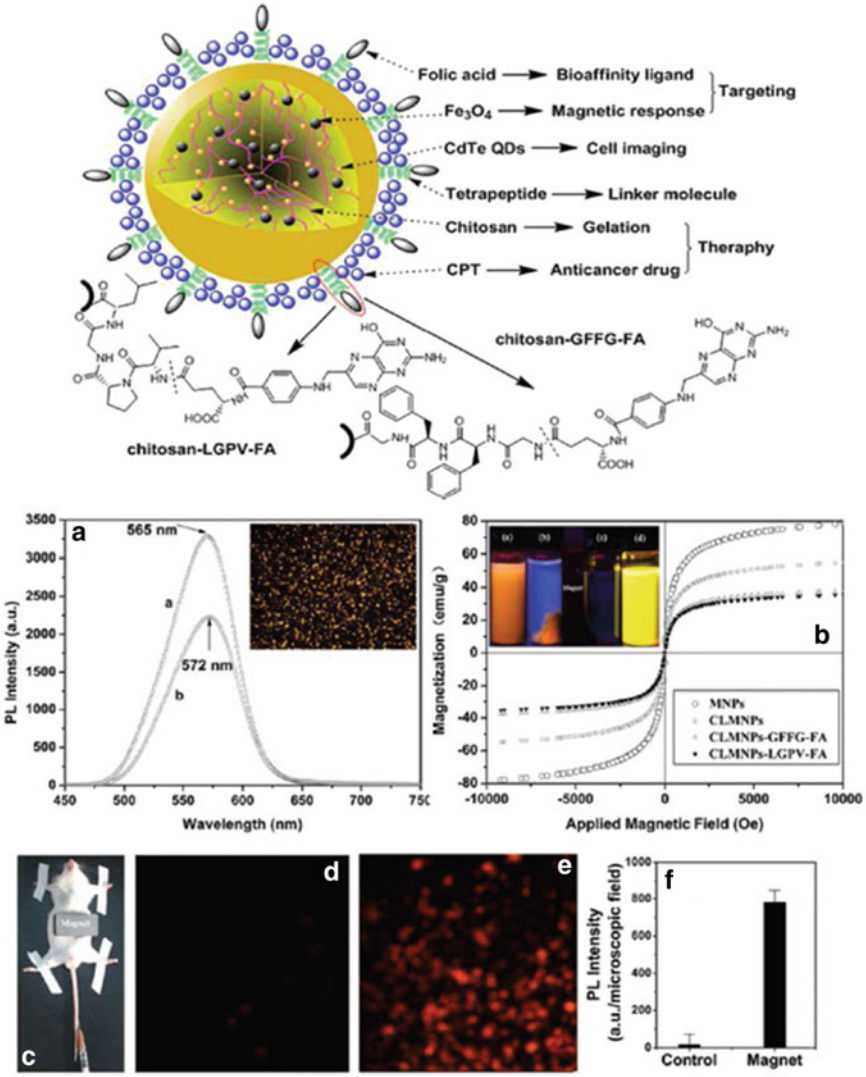

Fig. 16 Schematic illustration of the design of hybrid nanogel and (**A**) PL spectra of the as-prepared CLMNPs-GFFG-FA (**a**) and CLMNPs-LGPV-FA (**b**); (**B**) VSM magnetization curves of Fe3O4MNPs, CLMNPs, CLMNPs-GFFG-FA, and CLMNPs-LGPV-FA in applied magnetic field at 305 K. The inset in left top shows photograph taken under a 365 nm UV lamp: (**a**) CLMNPs, (**b**) CLMNPs-GFFG-FA, (**c**) Fe3O4MNPs, (**d**) TGA-capped CdTe QDs in deionized water. (**b**) and (**c**) are attracted by a permanent magnet. (**C**) Male S-180 sarcoma-bearing Kunming mouse being guided with a magnet after the CLMNPs-GFFG-FA copolymer was injected into the bloodstream by tail vein. (**D**, **E**) Representative fluorescence microscope images of the tumor slices induced without (**D**, control experiment) and with (**E**) magnet. "Adapted with permission from [117]. Copyright (2012) American Chemical Society"

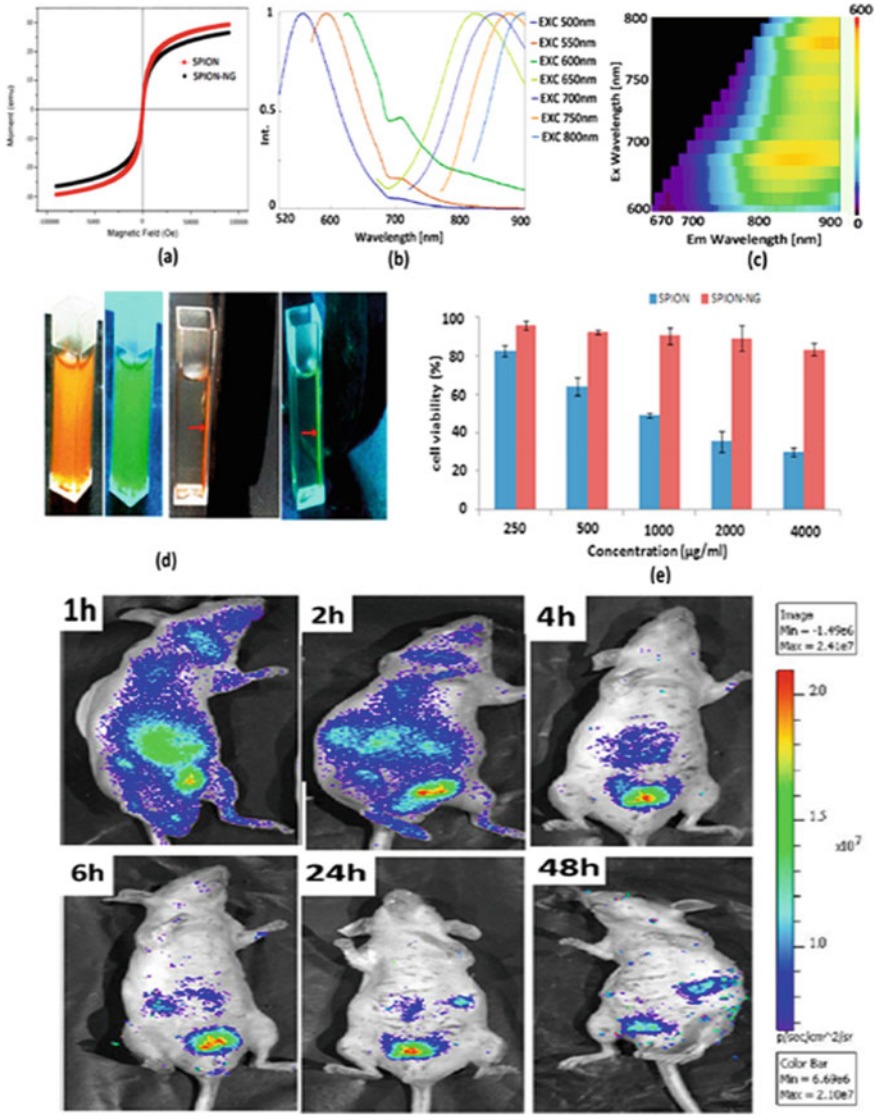

Fig. 17 VSM graph of SPION and SPION-NG (**a**). Excitation wavelength-dependent photoluminescent spectra of the SPION-NG under aqueous conditions at different excitations on visible region (500–800 nm) (**b**). Three-dimensional photoluminescence contour plot of SPION-NG at NIR region. **c** Magneto-fluorescent nature of SPION-NG under UV light excitation of 368 nm using water as the solvent (**d**). Cellular viability of SPION and SPION-NG having different concentrations (250–4000 μg/mL) (**e**). "Adapted with permission from [118] Copyright (2019) American Chemical Society"

Recently, Vijayan et al. have reported a magneto-fluorescent nanogel (SPION-NG) based on intrinsically fluorescent polymer poly-(ethylene glycol-co-maleic acid-co-glycine) and superparamagnetic iron oxide nanoparticles (SPION) [118].

The magneto-fluorescent nanogel was prepared by adding the SPION particles during the crosslinking of the fluorescent polymer with a cross-linker N, N-Dimethylaminoethyl methacrylate (Fig. 17). The prepared nanogel was exhibiting core–shell morphology with particle size around 80 nm. The intrinsic fluorescence characteristic of the nanogel was used to monitor the internalization of the nanogel in breast cancer cell Hela. Magnetic hyperthermia was utilized (due to the presence of SPION in the core of the nanogel) to demonstrate the therapeutic potential of the nanogel in cancer cells. Furthermore, the in vivo fluorescence imaging on mice has revealed favorable characteristics for bioimaging such as near IR imaging (having the highest tissue penetration) and lack of toxicity inside the body.

5 Conclusions and Future Perspectives

Multifunctional nanogels, especially those with magnetic and fluorescence characteristics, have immensely contributed in the area of nanomedicine. The multifunctional nature of them greatly helped to improve the efficiency of therapy and diagnostics for diseases like cancer. Some of the properties of nanogels such as higher water content, availability of versatile surface functional group, and biocompatibility makes it an ideal carrier toward theranostic applications. The design of the nanogels should be carefully controlled in order to accomplish the incorporation of sufficient amount of the fluorescent and magnetic moieties. The magnetic moieties present in the nanogels can be exploited for MRI imaging and magnetic hyperthermia. The fluorescent moieties present in the nanogel can be utilized for NIR imaging. Combination of both of this technique will be highly useful for nanotheranostics. The stimuli responsive (pH, temperature, and redox potential) linkages present in the backbone of the nanogel endow the smart and controllable delivery of the cargo at the region of interest. Even though they have many such advantages for nanomedicine, still they suffer from some major drawbacks such as scalability and toxicity issues caused from the external fluorescent and magnetic labels. There should be an ideal balance of the functional performance of these multifunctional nanogels with biocompatibility to ensure the successful translation of them from lab to clinics. Development of nanogels with innate imaging potential which does not require any external fluorescent and magnetic labels could be a good strategy to improve the biocompatibility of these multifunctional nanogels. A multidisciplinary collaborative effort which includes scientists, engineers, and physicians are clearly required to accomplish this goal. Possibly, the coming decade may witness more of this kind of a strategy which

could accelerate the process of multifunctional nanogel-based product development in clinics. Hence, still there is a long way to go for the successful clinical translation of these multifunctional nanogels in medicine.

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Chapter 5
Magnetic Glyconanoparticles for Biomedical Applications

V. Prajitha, K. P. Jibin, Jesiya Susan George, V. R. Remya, and Sabu Thomas

1 Introduction

The traditional view of carbohydrate polymers as nature's energy source (starch and glycogen) and structural materials has expanded to utilize various applications in biomedical field. Glycopolymers, synthetic sugar-containing polymers, possess a non-carbohydrate backbone but carrying carbohydrate moieties as a pendant or terminal end. Glycopolymers (Fig. 1) are increasingly attracting the scientists due to their role as biomimetic analogues and their potential for commercial applications [1].

There are different polymerization methods which have enabled the synthesis of glycopolymers featuring a wide range of controlled polymer chain architectures and functionalities.

Methodologies for the synthesis of glycopolymers can be generally classified (Fig. 2) into two main categories:

In general, the chemical modifications of preformed polymers with sugar-containing reagents method frequently result in glycopolymers having fewer regular structures because of incomplete reactions due to steric hindrance of macromolecular chains [2]. Therefore, it is often better to use polymerizations of sugar-carrying monomers for synthesizing linear glycopolymers of well-defined architectures.

V. Prajitha · K. P. Jibin · J. S. George · V. R. Remya · S. Thomas (✉)
International and Inter University Centre for Nano Science and Nanotechnology, Mahatma Gandhi University, Kottayam, Kerala 686560, India
e-mail: sabuthomas@mgu.ac.in

V. Prajitha · K. P. Jibin · J. S. George · S. Thomas
School of Chemical Sciences, Mahatma Gandhi University, Kottayam, Kerala 686560, India

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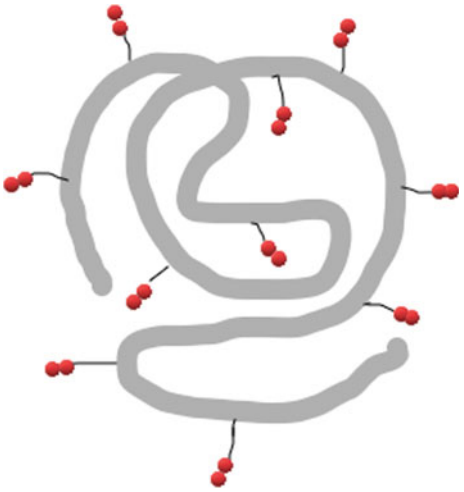

Fig. 1 Schematic illustration of glycopolymer

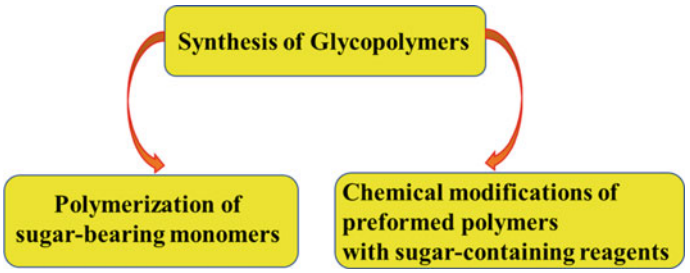

Fig. 2 Classification of synthesis Glycopolymers

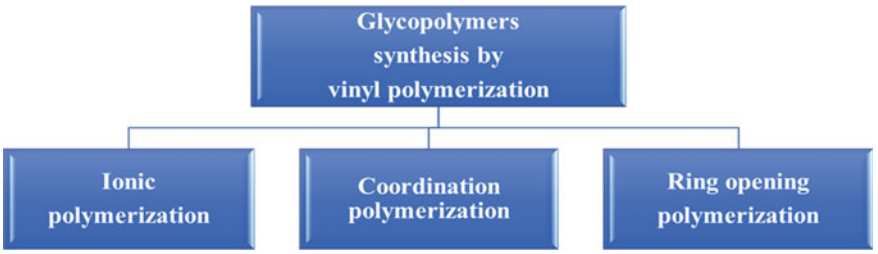

Fig. 3 Synthesis via vinyl polymerization

1.1 Synthesis of Glycopolymers

Ionic polymerization is a chain polymerization in which active centres are ions or ion pairs.

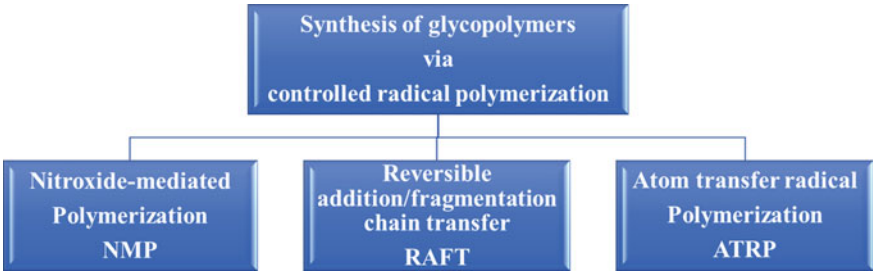

Fig. 4 Synthesis via controlled radical polymerization

Ionic polymerization is an alternative to radical polymerization to obtain well-defined polymers. Generally, ionic polymerization is divided into two categories [3].

(A) Cationic
(B) Anionic.

Cationic polymerization is in which kinetic chains carriers are cations [4]. The types of monomers necessary for cationic polymerization are limited to olefins with electron donating substituents and heterocycles.

Like cationic polymerization, anionic polymerization is also highly selective with respect to the possible monomers. This is limited to vinyl monomers possessing electron withdrawing groups such as nitrile, carbonyl and phenyl groups. Anionic polymerization is very sensitive to oxygen and generally requires aprotic solvents.

1.1.1 Synthesis of Glycopolymers via Controlled Radical Polymerization

The RAFT polymerization is a reversible deactivation radical polymerization (RDRP). The RAFT is a versatile technique that utilizes thio carbonyl thio compounds such as dithioester as mediating agents. It is one of several kinds of controlled radical polymerization [5]. It makes use of chain transfer agent in the form of a thiocarbonyl thio compound to afford control over the generating molecular weight and polydispersity during a free radical polymerization.

Trinadh et al. synthesized glycopolymers namely poly(acryl-2,3,4,6-tetra-*O*-acetyl-D-glucopyranoside) [poly(ATAGP)], poly[4-(acryloxy)butyl-2,3,4,6-tetra-*O*-acetyl-D-glucopyranoside] [poly(ABTAGP)] and poly(6-(acryloxy) hexyl-2,3,4,6-tetra-*O*-acetyl-D-glucopyranoside) [poly(AHTAGP)] were synthesized by introducing different alkyl chain spacer lengths between glucose moiety and polymer backbone and dodecyl alkyl chain at one terminal end of the macromolecular chain via the RAFT process. The resulted polymer pendant units,

2,3,4,6-tetra-*O*-acetyl-D-glucopyranosides, were deacetylated in the presence of sodium methoxide/chloroform/methanol mixture to obtain poly (acryl-D-glucopyranoside) (GP1), poly[4-(acryloxy)butyl-D-glucopyranoside] (GP2) and poly[6-(acryloxy)-hexyl-D-glucopyranoside] (GP3) glycopolymers, respectively. The effects of pendant spacer lengths of functional moieties were investigated. It was demonstrated that the cytotoxicity limits of osteoblast cells depend on the pendant spacer length of glucose moieties in glycopolymer on osteoblast cell adhesion, viability and proliferation were investigated in their study [6].

Dave et al. [7] synthesized homopolymers of AHTAGP and PEG-based di-block copolymers with the glycoacrylates ATAGP, ABTAGP and AHTAGP were prepared by the RAFT process using CPDTC and PEG-methyl ether (4-cyano-4-pentanoate dodecyl trithiocarbonate) as RAFT agents, respectively, with AIBN initiator. The resulting P(AHTAGP) and PEG-*b*-P(ATAGP), PEG-*b*-P (ABTAGP) and PEG-*b*-P(AHTAGP) di-block copolymers pendant 2,3,4,6-tetra-*O*-acetyl-D-glucopyranoside units were deacetylated in the presence of a sodium methoxide/chloroform/methanol mixture to obtain the P(AHGP) and PEG-*b*-P (AGP), PEG-*b*-P(ABGP) and PEG-*b*-P(AHGP), respectively.

1.2 Glyconanoparticles

Glyconanoparticles are the nanoparticles which contain functional carbohydrates or oligosaccharides [8]. Magnetic nanoparticles decorated glyconanoparticles have potential application in molecular imaging due to the presence of fluorescence properties [9–11]. Grafting of inorganic nanoparticles such as gold, iron oxide and quantum dots with glycopolymers was studied extensively as a targeting functionality in imaging and drug delivery applications [12].

1.2.1 Gold-Glycopolymer Nanoparticles

Glyco gold nanoparticles are the particles functionalized with sugars. Penadés et al. successfully synthesized highly stable and water-soluble gold glyconanoclusters by the reduction of gold salt in the presence of excess thiol-functionalized neoglycoconjugate (Fig. 5). These self-assembled monolayers form Au–S bond and form multifunctional and multivalent structure [13].

This single step method will help to prepare highly stable gold glyconanoparticles. A large number of scientific communities accepted this method and synthesized very interesting compounds using carbohydrate such as mannose, glucose and galactose [12, 14–17].

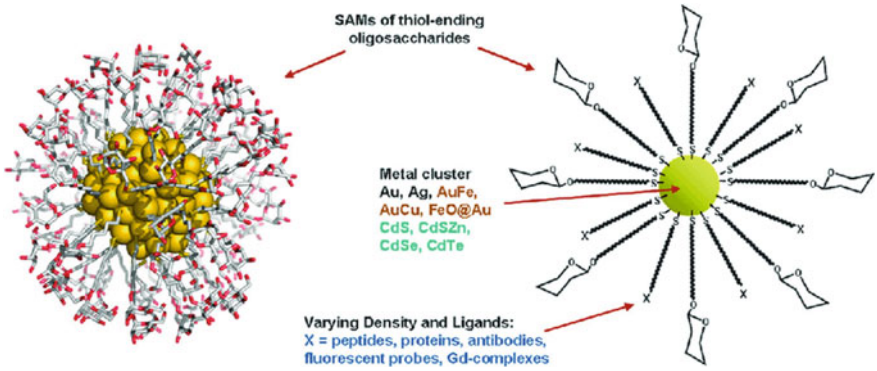

Fig. 5 Calculated structure for a gold glyconanoparticle bearing 5-mercaptopentyl-a-D-mannopyranoside and a schematic representation of the potential modifications which can be introduced on gold glyconanoparticles to obtain multifunctional and multimodal glyconanoparticles. (Reproduced with permission from Royal Society of Chemistry)

1.2.2 Iron Oxide-Glycopolymer Nanoparticles

Magnetic nanoparticles have a potential application in biomedical field such as magnetic resonance imaging (MRI), diagnosis, biosensors and targeted delivery. Surface modification of these magnetic particles shows a major role when it interacts with the biological system. Highly biocompatible and biodegradable carbohydrate moieties will improve the colloidal stability, and they can specifically recognize and interact with biomolecules such as nucleotides, vitamins, peptides, antibodies, hormones and lectins. Magnetic glyconanoparticles were synthesized via coprecipitation method [12, 18–20]. Penadés et al. synthesized magnetic glyconanoparticles starting from a mixture of Au and Fe salt in one step synthesis. This bimetallic Fe doped Au GNP has a potential application in magnetic resonance imaging [13]. Figure 6 represents the preparation of magnetic glyconanoparticles (MGNPs) and their conjugation with protein.

1.2.3 Quantum Dots-Glycopolymer Nanoparticles

Quantum dots has very good fluorescent properties, and glyco QD has potential application in the field of bio-imaging. Functionalization with carbohydrates will help to increase the cellular uptake of nanoparticles. Carbohydrate wrapped quantum dots could specifically bind cell surface of certain tissues [21]. Alifonso et al. conjugated CdSeS/ZnS QD and galactose via receptor mediated endocytosis. QD wrapped with *N*-acetyl lactosamine can be used as a fluorescent probe to study the interaction of galectin-3 and *N*-acetyl lactosamine [22]. Schematic representation (Fig. 7) of surface modification of QDs and their binding to lectins are shown below.

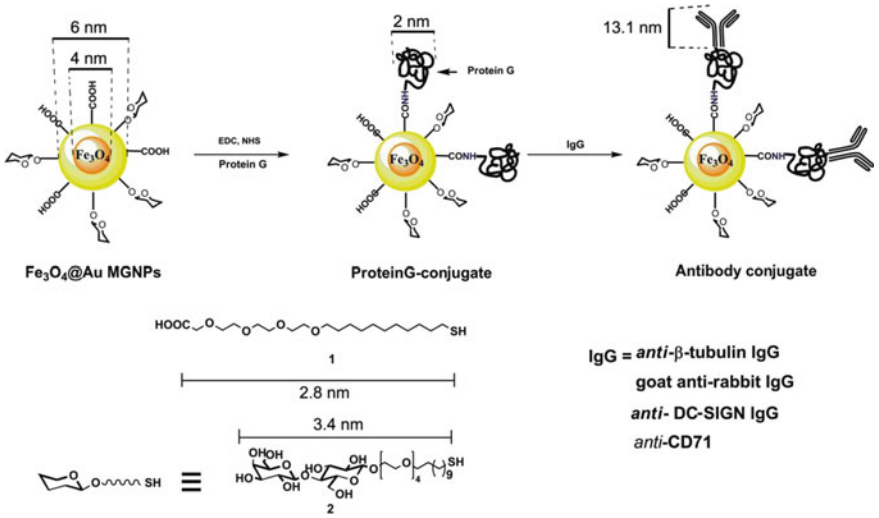

Fig. 6 Schematic representation of the preparation of magnetic glyconanoparticles (MGNPs) and their conjugation with protein G (protG-MGNPs) and antibodies (IgG@protGMGNPs) (Reproduced with permission from American Chemical Society)

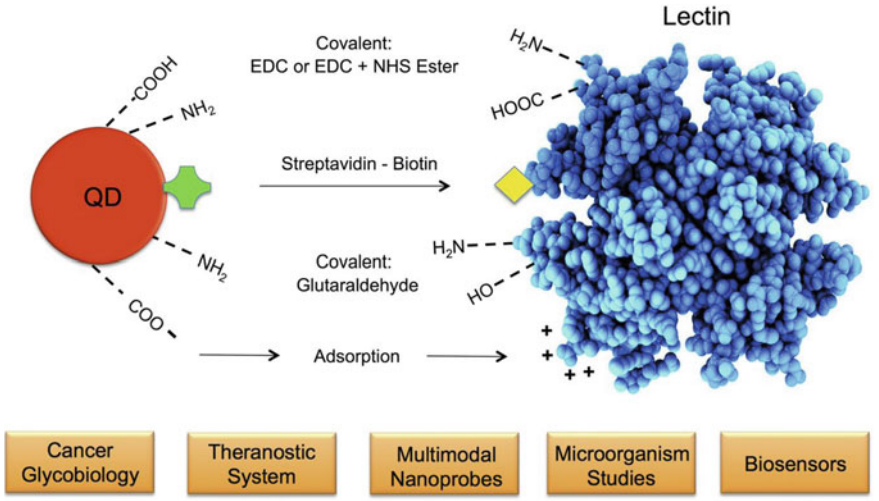

Fig. 7 Schematic representation of surface modification of QDs and their binding to lectins. (Reproduced with permission from Elsevier)

Presence of fluorescent properties and ability to make conjugation with biomolecules make quantum dots have a potential in biomedical field such as (i) Tumour glycobiology [23] (ii) Probes for cell labeling [24] (iii) Cell metabolism study [25] (iv) Lectin binding [26].

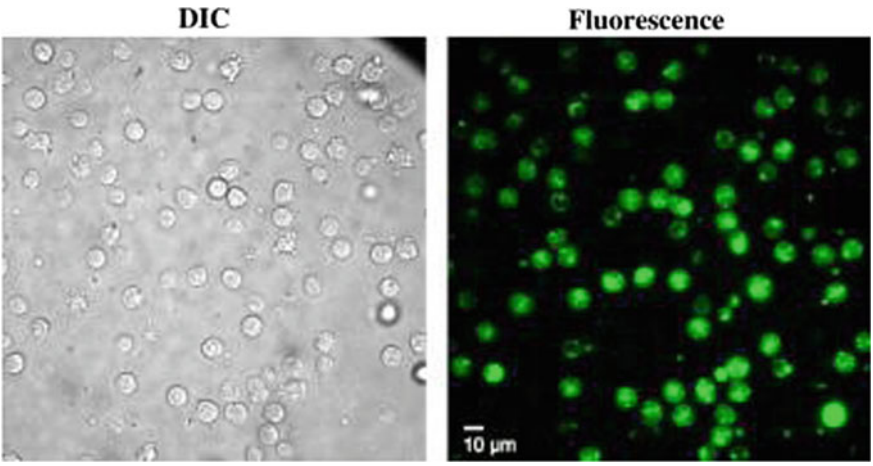

Fig. 8 Polyvalent lactosyl QDs (Lac-QDs) used for the fluorescent labelling of live leukocytes. (Reproduced with permission from Elsevier)

Yang et al. [26] studied the fluorescent properties (Fig. 8) of glyco-quantum dots by modifying with lactose and find out that it is an efficient fluorescent probe. Polyvalent lactosyl QD can assess the protein–carbohydrate interaction, and they can image the cellular activities of glycoproteins. These glyco QD has a potential in targeted drug delivery.

1.3 Glyconanoparticles in Drug Delivery

Nanoparticles incorporated biodegradable polymers such as glycopolymer micelles have potential application in cancer therapy. These glyconanoparticles have the ability to improve the bioavailability of anti-cancer drugs. They will improve the accumulation of drug in the tumour tissue via enhanced permeability and retention (EPR) effect [27, 28]. Lactose-functionalized nanoparticles incorporated saccharides such as β-D galactose, *N*-acetyl galactosamine have been studied for targeted liver cancer therapy. Figure 9 shows galactose decorated micelle preparation followed by UV radiation [29–31].

Yang et al. [30] explored the in vivo targetability and anti-tumour efficiency of multi-stimuli responsive glyconanoparticles. They have a potential use in controlled drug delivery and cancer Therapy (Fig. 10).

Yang et al. reported that self-assembled micelles from galactose-functionalized amphiphilic polycarbonate block copolymers have significant increase in antitumor activity in ASGP-R positive HepG2 cells as compared to HEK 293 cells [31]. Suriano et al. [32] show that the galactose-containing micelles can deliver doxorubicin ((DOX) a drug used for liver cancer treatment) more competent to

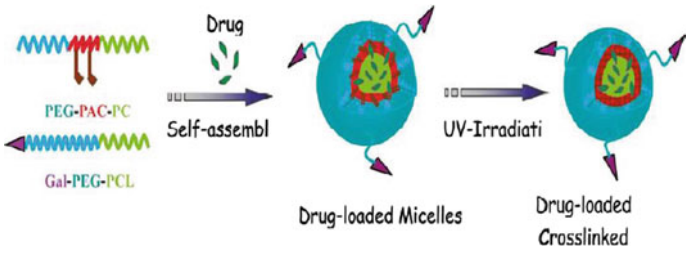

Fig. 9 Illustration on the preparation of Galactose-Decorated interfacially Crosslinked Biodegradable Micelles from PEGPAC- PCL and Gal-PEG-PCL Block Copolymers, Followed by UV Irradiation. (Reproduced with permission from American Chemical Society)

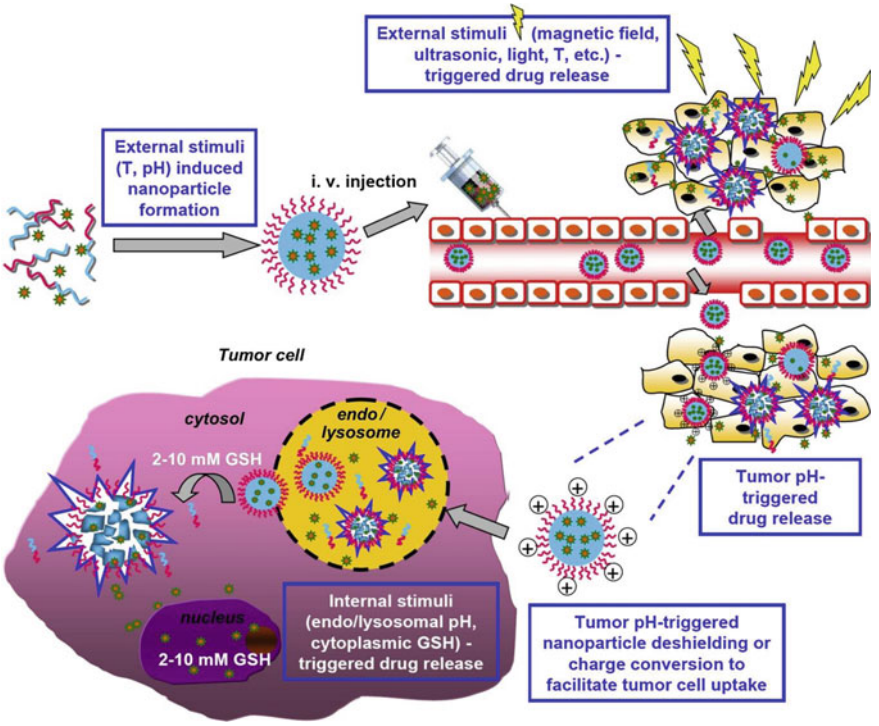

Fig. 10 Dual and multi-stimuli responsive polymeric nanoparticles as emerging controlled drug release systems. The two and more stimuli are applied as following: (i) application of an external stimulus such as temperature and pH to facilitate formation of nanoparticles; (ii) application of an external stimulus such as magnetic field, ultrasonic, light, and temperature to trigger drug release, which allows precision spatial, temporal as well as dose control over drug release at will through a remote apparatus; (iii) acidic tumor pH (6.5e 7.2) is utilized to trigger drug release and/or reverse shielding of nanoparticles at tumor site thereby enhancing tumor cell uptake of nanoparticulate drugs; and (iv) intracellular environments such as low pH in endo/lysosomal compartments and high redox potential in cytoplasm are utilized to improve intracellular drug release inside tumor cells (Reproduced with permission from Elsevier)

asialoglycoprotein receptors (ASGP-R) positive HepG2 liver carcinoma cells than in ASGP-R negative HEK293 human embryonic kidney cell lines. By using galactose-containing micelles, cytotoxicity of doxorubicin against HepG2 cells was increased significantly as compared to free DOX formulation and the glucose-containing micelles. Figure 11 shows the confocal image of cellular uptake of galactose-containing micelles. The galactose-containing micelles can be a potential carrier to target drugs particularly to liver tissues/cells [32].

Chen et al. reported a novel disulphide-linked glyconanoparticles (SS-GNs) readily obtained from the self-assembly of amphiphilic poly (ε-caprolactone)-graft-SS-lactobionic acid (PCL-g-SSLBA) graft copolymer for hepatoma-targeting intracellular delivery of anti-cancer drugs shown in Fig. 12.

Chen et al. discovered that disulphide-linked glyconanoparticles have very good hepatoma targetability and they can easily deliver and release anti-cancer drugs into the carcinoma cells (Fig. 13). Glyconanoparticles have excellent properties such as water solubility, biocompatibility, reduction-sensitivity and tumour-targetability. The high targetability of SS-GNs is due to the cluster glycoside effect [33]. These biocompatible glyconanoparticles provide an effective platform for targeted liver cancer chemotherapy [34].

Other than drug delivery, magnetic glyconanoparticles have application in bio-imaging due to the fluorescence properties, lectin binding, bio-sensor, etc.

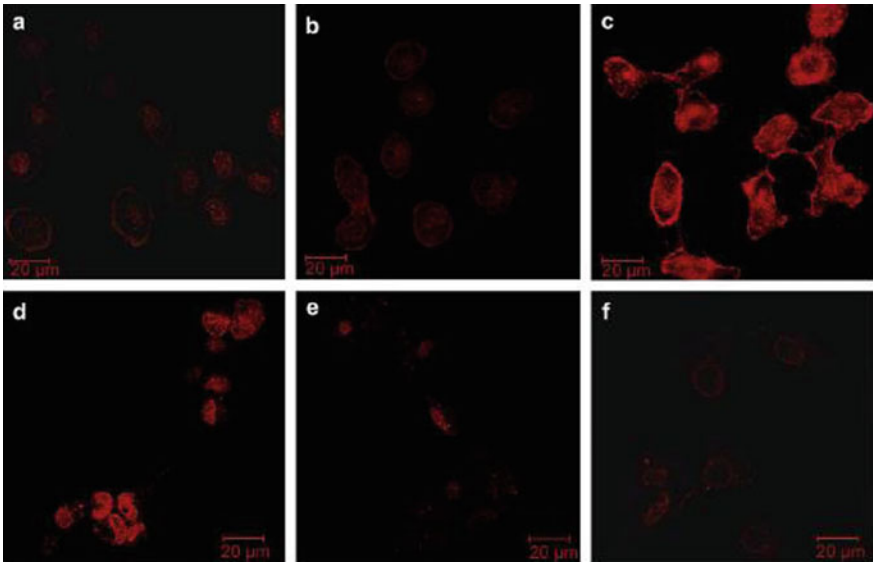

Fig. 11 Cellular uptake of galactose-containing micelles. Confocal images of HepG2 (a–c) and HEK293 (d–f) cells after incubated with (a, d) free DOX, (b, e) DOX-loaded glucose containing micelles and (c, f) DOX-loaded galactose-containing micelles for 3 h at a DOX concentration of 1 mg/L. Size of the scale bars: 20 mm. (Reproduced with permission from Elsevier)

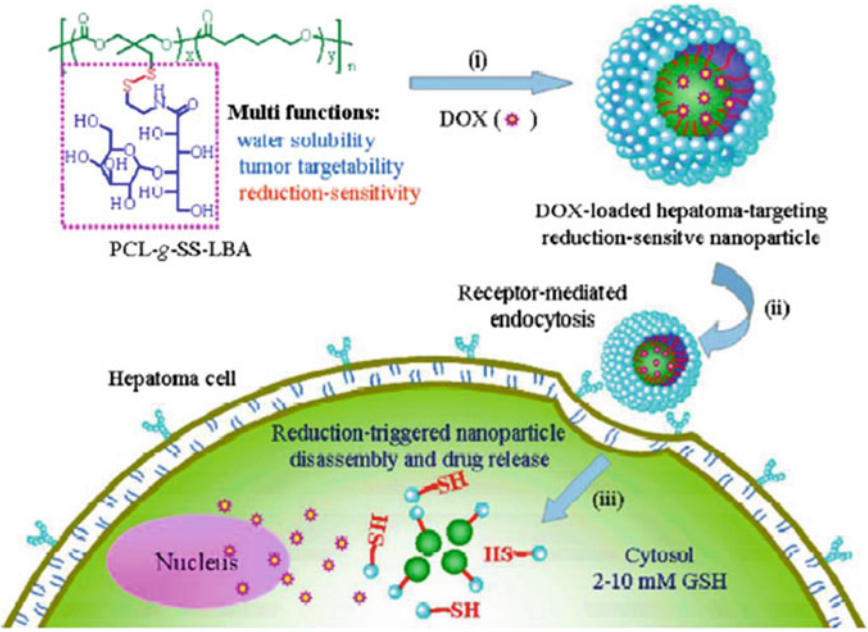

Fig. 12 Illustration of Disulfide-Linked Glyco-Nanoparticles (SS-GNs) for Hepatoma-Targeting Intracellular Delivery of Anticancer Drugs (i) SS-GNs (ii) SS-GNs are efficiently taken up by hepatocellular carcinoma cells via the receptor-mediated mechanism; and (iii) SS-GNs quickly release payloads into the cytosols and cell nuclei due to shedding of saccharide shells. (Reproduced with permission from American Chemical Society)

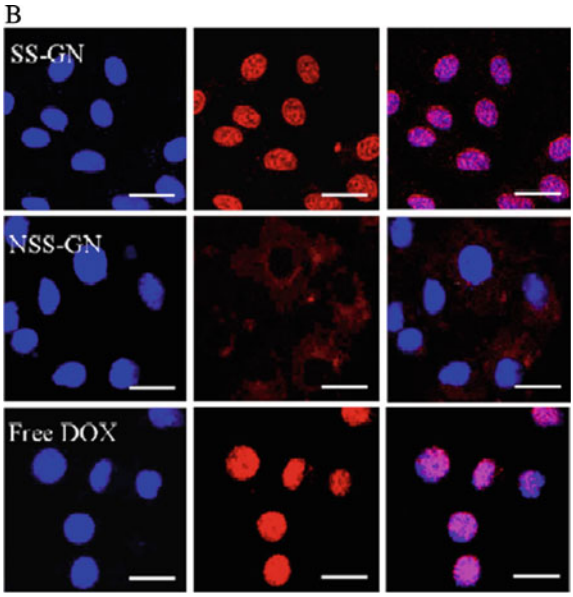

Fig. 13 Cellular uptake and intracellular release of DOX into HepG2 cells following 4 h incubation. (B) CLSM images of HepG2 cells incubated with DOX-loaded nanoparticles or free DOX (5 μg/mL). For each panel, the images from left to right show cell nuclei stained by DAPI (blue), DOX fluorescence in cells (red) and overlays of the two images. (Reproduced with permission from American Chemical Society)

2 Conclusion

Glyconanotechnology has major applications in various fields such as drug delivery, bio-imaging, lectin binding, materials for controlled cell culture, surface modifiers, artificial tissues and artificial organic substrates due to their hydrophilic character and ability of compatibility with biomolecules.

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Chapter 6
Magnetic Nanoparticles for Hyperthermia a New Revolution in Cancer Treatment

Sandhya Gopalakrishnan and Kannan Vaidyanathan

1 Introduction

In the 1900s, infectious diseases were responsible for the major share of disease deaths. By the next century, most of these diseases were brought under control. In the current generation, cancer and heart diseases account for the major share of disease burden. Cancer is probably the most dreaded disease of the present century. Several treatment methods have been tried, but we have not been successful in eliminating cancer. Chemotherapy is one of the well-known modes of cancer therapy. Traditional chemotherapeutic agents had limited success, and some of them were also highly toxic. Hence, there is a need for newer modalities of cancer chemotherapy.

Magnetic nanoparticles (NPs) have a magnetic core, biocompatible coating, and surface functionalizations. Such a structure allows integration of targeting agents, chemotherapeutic and biotherapeutic agents. They have theranostic properties [1].

2 Hyperthermia Therapy

It is well-known that cancer cells die when exposed to higher temperatures. This is the basis of hyperthermia therapy, which is receiving increasing attention. The body is exposed to higher temperatures. In the case of cancer, local hyperthermia is used.

Heat can be produced by different means, like microwave, radiofrequency, ultrasound or magnetic hyperthermia. For smaller tumors, radio-ablation is used by

S. Gopalakrishnan (✉)
Department of Prosthodontics, Government Dental College, Kottayam, Kerala, India

K. Vaidyanathan
Department of Biochemistry and Head Molecular Biology, Amrita Institute of Medical Science and Research Center, Kochi, Kerala, India

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a technique known as superficial hyperthermia, where the tissue is exposed to radiation. If needles are inserted into the tissues, it is known as interstitial hyperthermia [2–4].

Hyperthermia kills cells directly, but the more significant effects are produced when it is combined with other modalities of cancer therapy [5]. It increases blood perfusion as well as produced hyperbaric conditions, proving to be toxic to cancer cells [6]. There is hypothesis that the size of cancer cells may decrease with heat. However, it should be remembered that hyperthermia is not specifically toxic to cancer cells; it can also damage normal cells. Hence, hyperthermia is not without side effects. Side effects of heat include surface burns, swelling, blood clots, and bleeding complications [6]. Systemic toxicities including cardiovascular toxicity and systemic shock syndrome may occur [7]. The most important aspect is to be able to control the temperature inside the cells/body.

Targeted radiotherapy refers to delivery of higher dose of radiation to cancer cells without causing damage to nearby tissues. It is used in many types of cancers, including head and neck, brain, lung, and prostate cancers. Hyperthermia assists this process significantly [8].

Magnetic hyperthermia may trigger differentiation of cancer cells, preventing progression of cancer [9]. Dendrimers can form effective hybrid platforms with magnetic nanoparticles to form the basis of cancer therapy [10].

3 Magnetic Nanoparticles

Magnetic nanoparticles (MNPs) are a group of nanoparticles whose properties can be modified by application of magnetic fields. MNPs are particular in that they produce controlled increase in temperature. Temperature distribution can be controlled by the velocity, size, and distribution of MNPs within the body [11, 12].

Upon application of external magnetic field, MNPs are able to convert electromagnetic energy to thermal energy and thereby increase the temperature [13]. The increase in temperature enhances tumor oxygenation and chemo- and radio-sensitivity. The net effect is shrinkage in tumor size [14]. Heat may be dissipated as well, especially when alternating magnetic current is applied. Nanoparticles, including magnetic NPs, bring about thermal ablation of tumors. They have advantages over conventional heating methods [15].

Utilizing intra-tumoral Fenton reaction for cancer therapy is a new field known as chemodynamic therapy. The acidic pH of tumor environment is not exactly suited for normal Fenton reaction and hence requires enhancement [16].

Suitable methods need to be developed to produce localized hyperthermia and targeted release of chemotherapy drug. Many modifications of the basic technology have been investigated, and further, methods may need to be evaluated [17, 18].

Magnetic hyperthermia has been useful in the treatment of oral cancer [19, 20]. When exposed to alternating magnetic field, certain NPs can generate heat through hysteresis [21]. This phenomenon forms the basis of cancer therapy using MNPs

[22]. Multifunctional magnetic gold nanomaterials have been used for the treatment of cancer [23–25].

4 Superparamagnetic Nanoparticles

Magnetofection using superparamagnetic nanoparticles (SPIONs) has been used as an alternative to gene therapy in human breast cancer MCF7 cells for gene transfer [26]. Hyaluronic acid-modified mesoporous silica-coated superparamagnetic iron oxide particles are used for targeted cancer therapy [27].

5 Multifunctional Nanoparticles

Functionalized magnetoparticles sensitize tumors to X-rays and protons and act as radio-enhancers. These are thus used in cancer therapy [28]. Multifunctional nanoparticles (MFNPs) have wide theranostic potential; some examples of studies where they have been used are given below [29].

Mesoporous polydopamine nanosponges on a multifunctional platform have been used for the treatment of cancer [30]. Fe_3O_4-TMZ-ICG MNPs are produced by incorporating iron oxide NPs with temozolomide (TMZ) and indocyanine green (ICG). These agents enhance apoptosis-mediated death through various genes involved in the pathway. Such selective chemo-phototherapy using these agents has found applications in the treatment of brain cancer [31].

Core-shell-structured iron carbide ($Fe_5C_2@Fe_3O_4$) nanoparticles (NPs) produce reactive oxygen species (ROS), through the catalysis of the Fenton reaction. Normally, ROS-mediated therapy is an inefficient process, but these agents have showed great promise because of high efficiency and high specificity [32]. Biocompatible core-shell magnetic nanocomposite based on cross-linked chitosan hydrogels (using synthetic terephthaloyldiisothiocyanate as a cross-linker) is used for cancer therapy based on in vitro hyperthermia [33].

MFNPs have also been formed by genetically manipulating NK cells by genetic engineering and conjugating them with magnetic and fluorescent NPs. They have enhanced cancer cytotoxicity [34]. Silica-coated iron oxide NPs (SIO-MNPs) have enhanced radio-sensitivity in breast cancer cells [35]. Graphene oxide NPs kill cancer cells better when they are multifunctional, incorporated with iron oxide NPs and hyaluronic acid. This enables the use of magnetic hyperthermia and kills cancer cells better [36]. An oral drug delivery system [polyacrylic acid (PAA) and chitosan (CS) on Gd^{3+} -doped mesoporous hydroxyapatite nanoparticles (Gd-MHAp NPs)] has been developed which might be useful for orthotopic colon cancer therapy [37].

MFNPs have been used in the treatment of brain cancer [38]. Multifunctional iron oxide nanocomposites have been used for imaging-guided photothermal

therapy of cancers [39]. Certain functionalized NPs are used for fluorescence imaging-guided photothermal therapy [40].

Magnetic NPs have also been used for imaging-guided immunotherapy [41]. MFNPs have also been used for metastatic cancers [42]. Cisplatin-functionalized NPs have been used for the treatment of breast cancer [43]. Some MFNPs [Fe_3O_4@KCTS, a core-shell type of magnetic nanoparticles, prepared by activating Fe_3O_4 with carbodiimide and cross-linking it with α-ketoglutarate chitosan (KCTS)] are also used for cancer detection [44]. Advantages include excellent loading efficiency, real-time monitoring, and improved cargo bioavailability and bioselectivity [45].

A triple-modal superparamagnetic iron oxide (Fe_3O_4), IR780, doxorubicin (DOX), and perfluoropentane (PFP) entrapped poly-lactide-co-glycolide (PLGA) nanoparticles (IR780/Fe_3O_4@PLGA/PFP/DOX NPs) have been used experimentally for breast cancer treatment [46].

Doxorubicin-loaded magnetic mesoporous silica nanoparticles (ND-MMSNs) have been used for targeting glioma cells. The platform has been used for imaging as well as therapeutic purposes [47].

PEGylated branched gold (Au)-iron oxide (Fe_3O_4) Janus nanoparticles (JNPs) are used for simultaneous trimodal imaging and photothermal therapy of cancer cells [48].

Exceedingly small magnetic iron oxide nanoparticles (ES-MIONs) (<5 nm) are used for magnetic resonance imaging (MRI) as well as for therapeutic purposes in cancer in experimental animals [49].

Dual surfaced dumbbell-like gold magnetic nanoparticles (Au–Fe_3O_4) are used for targeted aptamer delivery, and these are used as carriers for cancer hyperthermia therapy [50].

Superparamagnetic iron oxide particles have been successfully implemented for the treatment of gastric cancer [51].

Magnetically responsive microbubbles are used in the treatment of pancreatic cancer. Microbubbles are lipid or polymer stabilized gas filled particles [52].

Magnetically and thermally sensitive poly(*N*-isopropylacrylamide) (PNIPAAm)/Fe_3O_4–NH_2 microgels encapsulated with curcumin (Cur) are used as controlled release cancer therapeutic drugs [53].

Colorectal cancer with liver metastasis has been treated by hybrid functionalized magnetic-gold NPs [54]. Magnetic MFNPs are used in the treatment of prostate cancer [55, 56] and bladder cancer [57].

Core-shell PB@MIL-100(Fe) dual metal-organic-frameworks (d-MOFs) nanoparticles are used for theranostic cancer therapy [58]. MFNPs enables Fenton reaction assisted photodynamic therapy [59].

Magnetotactic bacteria are aquatic organisms having strong biomedical applications. This is because of their hyperthermia effect, affecting cancer cell proliferation [60].

Stable hybrid nanobiocatalyst is formed when biomimetic silica (Si) nanoparticles are entrapped with Horseradish Peroxidase and magnetic nanoparticles. These NPs have wide applications in cancer therapy [61]. The degradable poly

(AA-co-DMA) nanohydrogels with surface-tailorable functionalities are used with nanomaterials and drug molecules for cancer therapy [62].

Because of the superparamagnetic, biocompatible and biodegradable properties, iron oxide NPs are used in the treatment of breast cancer [63]. A multifunctional drug-loaded nanosystem (F/A-PLGA@DOX/SPIO) has been used in the treatment of lung cancer [64].

MFNPs are also used as radiosensitizers in the radiation therapy and imaging [65]. Up-conversion MFNPs are used for photodynamic therapy [66].

Copper sulfide NPs have wide applications in therapeutics [67].

SPIONs with gold NPs have been used for phototherapy [68].

Graphene oxide nanosheets are loaded by magnetic iron oxide nanoparticles (mGO), followed by the technique of layer-by-layer (LbL) self-assembly for the production of chitosan/sodium alginate functionalized mGOnaocomposites. They are used in targeted anticancer drug delivery and photothermal therapy [69].

A synergistic treatment platform was developed with plasmonic-magnetic hybrid nanoparticle (lipids, doxorubicin (DOX), gold nanorods, and iron oxide nanocluster (LDGI))-loaded mesenchymal stem cells (MSCs) for the imaging and treatment of triple negative breast cancer [70].

Cold atmospheric plasma (CAP) combined with magnetic NPs has been used in the treatment of lung cancer [71].

Magnetic nanogels made of thermosensitive and biocompatible polymers and core-shell nanoparticles with a magnetic core and molecularly imprinted polymer shell are both used for cancer therapy [72].

Dual-responsive multifunctional magnetic complex micelle (sPEG/HA/CSO-SS-Hex/Fe_3O_4/GA) consisting of reducible hexadecanol-modified chitosan oligosaccharide polymer micelle (CSO-SS-Hex) coated with hyaluronic acid (HA) and DCA grafted sheddable PEG-PLL (sPEG) copolymers and loaded with gambogic acid (GA) and Fe_3O_4 nanoparticles is used for the treatment of triple negative breast cancer [73].

Polymer-coated gold-ferric oxide superparamagnetic nanoparticles have theranostic applications [74].

Hydrophilic graphene-based yolk-shell magnetic nanoparticles functionalized with copolymer pluronic F-127 (GYSMNP@PF127) produces hyperthermia and is used for cancer therapy [75].

Multifunctional iron–gold alloy nanoparticles are used for combined hyperthermia and dual stimuli-responsive drug delivery [76]. Poly lactic-co-glycolic acid (PLGA)-modified magnetic nanoplatform was synthesized with iron oxide NPs for enhanced apoptosis and therapy in human brain cancer [77].

Functionalized boron nitride nanotubes (BNNTs) are efficient tools for magnetohyperthermia treatment [78].

Gold MFNPs have significant theranostic properties. They have autophagy-based chemotherapeutic applications [79].

Nearly monodispersed magnetic Fe_3O_4@MTX-LDH/Au nanoparticles (NPs) containing methotrexate (MTX) produce hyperthermia and are used in cancer therapy [80].

The chemotherapeutic drug, sorafenib with PVA/SPIONs showed better anti-cancer efficiency than free sorafenib in the treatment of hepatocellular carcinoma [81].

Amphipathic chitosan-based nanomicelle with doxorubicin and SPIONs are used in the treatment of metastatic breast cancer [82].

Hydroxyapatite-coated iron oxide NPs are used for producing magnetic hyperthermia for the treatment of cancer cells [83].

Curcumin-loaded magnetic alginate/chitosan nanoparticles were used for therapy in MDA-MB-231 breast cancer cells [84].

6 Hybrid Nanoparticles

Hybrid NPs are formed by integrating Gd doped silicon nanoparticles (Si–Gd NPs), chlorine e6 (Ce6), doxorubicin (DOX), zeoliticimidazolate framework-8 (ZIF-8), poly(2-(diethylamino)ethyl methacrylate) polymers (HOOC-PDMAEMA-SH), and folic acid-polyethylene glycol-maleimide (MaL-PEG-FA) into one single nanoplatform. Such hybrid NPs are good theranostic agents [85].

Her2 functionalized gold-nanoshelled magnetic hybrid NPs are used as theranostic agents for dual-modal imaging and photothermal therapy of breast cancer cells. The advantages are non-invasive diagnosis and used as adjuvant therapy in SKBR3 cells [86].

7 Synthesis of Magnetic NPs

Production of sub-10 nm SPIONs is a challenging task. Several methods are available for the same. One such involves poly(ethylene glycol) (PEG) reactor adsorbed onto reduced graphene oxide nanosheets (rGO) via the microwave hydrothermal route [87].

Microrobots are small, non-invasive and can be subjected to robotic control. They are important vehicles for targeted therapy. Degradable hyperthermia microrobot (DHM) containing poly(ethylene glycol) diacrylate (PEGDA) and pentaerythritoltriacrylate (PETA) and magnetic Fe_3O_4 nanoparticles (MNPs) and 5-fluorouracil (5-FU) are useful agents for targeted therapy and hyperthermia [88].

8 Other NPs Producing Hyperthermia

Magnetic NPs are the main agents producing hyperthermia. However, there are some other NPs which also produce hyperthermia and hence may be used for the treatment of cancer.

Hyaluronic acid-based NPs include micelles, polymersomes, hydrogels, and nanoparticles. They bind to receptors over-expressed in certain cancers. They are important platforms for hyperthermic cancer therapy [89].

Near-infrared (NIR)-based iron oxide nanomaterials (NIR-IO) are excellent vehicles for tumor ablation and were found to have good biocompatibility and low cytotoxicity. They have great potential as theranostic agents in cancer [90].

Reactive oxygen species (ROS)-producing NPs have the natural ability to produce hyperthermia. Indeed magnetic NPs can also produce ROS by Fenton reaction and otherwise. This has been discussed earlier in this chapter [91].

Others include glutathione producing particles including ultra-small gadolinium oxide NPs. These are used for CT/MR-guided photothermal and radio-combination cancer therapy [92]. Iron-doped copper sulfide NPs also can produce hyperthermia and are used for MRI [93]. Iron-containing multifunctional nanozymes kills tumor cells efficiently [94]. Carboxymethyl chitosan (CMCS) is used as a nanodelivery system carrier for sustained intracellular release of rose bengal (RB) and doxorubicin (DOX) to achieve combinational drug treatment [95].

Magnetoliposomes containing $MgFe_2O_4$ nanoparticles are used in cancer therapy, allowing combined magnetic hyperthermia and chemotherapy [96]. Co-delivery system of (DOX/MEL)-loaded citric acid-functionalized Fe_3O_4 magnetic nanoparticles (CA-MNPs) is highly capable to be used in magnetically targeted cancer therapy [97].

Silk-PEI nanoparticles (SPPs) and magnetic-silk/PEI core-shell nanoparticles (MSPPs) were used for targeted delivery of c-myc antisense oligodeoxynucleotides (ODNs) into MDA-MB-231 breast cancer cells [98]. Gold nanocages (AuNCs) modified with hyaluronic acid (HA) and conjugated with anti-Glypican-1 (anti-GPC1) antibody, oridonin (ORI), gadolinium (Gd), and Cy7 dye have been used for the treatment of pancreatic cancer [99].

Folic acid (FA)-conjugated poly (lactic-co-glycolicacid) (PLGA)-polyethylene glycol (PEG) nano-noisome has been used for the treatment of cervical cancer [100]. Indocyanine green (ICG)-conjugated NPs are used for photothermaltumor therapy [101].

9 Magnetic Liposomes

Magnetic liposomes are used in cancer therapy [102]. Bacterial magnetosomes have been developed recently co-loaded with siRNA and doxorubicin, using polyethylineamine as a cross-linking agent. These nanocarriers are used in cancer therapeutics [103]. Magnetic nanoclusters have been also used for delivery of cisplatin for chemotherapy [104].

Neoadjuvantnano-photothermal therapy (NNPT) has been used in breast cancer treatment. When it is done before surgery, NNPT is found to improve the benefits of surgery [105].

Multifunctional nanohybrids have various applications in improving drug delivery of magnetic NPs [106]. Gadolinium-based nanoplatforms have been used for cancer therapy [107].

Superparamagnetic nanoparticles (SPIONs) have been coated with the amphiphilic copolymer INU-LA-PEG-FA and loaded with doxorubicin (DOXO-SPIONs) to function as smart agents for colon cancer therapy [108].

10 Ferroptosis

Iron-dependent cell death mediated by lipid peroxidation is known as ferroptosis. Fenton reaction produces reactive oxygen species, which also contributes to lipid peroxidation. Iron-based NPs can produce ferroptosis [109]. Ferroptosis is also used in the treatment of brain tumors [110]. Ferroptosis contributes to the hyperthermia in producing the effects of magnetic NPs.

11 Challenges

The main challenge of magnetic NPs is toxicity itself. They can produce cytotoxicity, pyrogenicity, genotoxicity, in vitro hemolysis, skin reactivity, and acute and chronic systemic toxicity in experimental animals [111]. The other disadvantage is a lack of sensitivity toward tumor tissues [112].

12 Conclusion

Various magnetic NPs have been described in the recent years. A complete description of the complete armamentarium of these species is beyond the scope of any publication. However, we have tried to focus on the latest and most important of this important group of NPs. The most important mechanism by which magnetic NPs work is by producing hyperthermia. In addition, ROS production and Fenton reaction, as well as ferroptosis, contribute to the same. There are other NPs which produce hyperthermia, but magnetic NPs are the most important among them. Future years shall reveal newer magnetic NPs, including MFNPs, with better functionalities. Indeed, as is the case with any NP, the main issue shall remain as toxicity. Once, we solve the toxicity paradox, magnetic NPs shall become one of the most important tools available to the physician for the treatment of a variety of cancers.

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Chapter 7
Magnetic Nanoparticles for Cancer Treatment

Subin Balachandran

1 Introduction

Cancer is considered to be one of the most dreadful diseases throughout the world. The number of patients suffering from cancer and other cancer-related diseases increases day by day. The major reasons for this include disease identification in later stages and various side effects during chemotherapy. So, oncology researchers are highly interested in discovering novel tool and techniques for the early diagnosis of cancer and also reducing the profound side effects of existing chemotherapeutics. Out of the different investigations and innovations in the area of cancer research, targeted therapy is considered to be more attractive.

Targeted therapy mainly focused on precisely identifying tumour cells using specific markers in them and further delivering chemotherapeutics directly into these cells. These targeted therapies can easily be done with nanotechnology combined chemotherapy. Nanotechnology had greatly contributed for revolutionising cancer therapy and diagnosis. Nanoparticles, (NP) when modified and tagged with specific cellular markers, can easily circulate through blood and can reach the target organs. When chemotherapeutics is loaded to these modified nanoparticles, drugs can be easily delivered to their targets without affection normal, non-target cells. Magnetic nanoparticles (mNPs) due to their supermagnetic potential provide an added advantage in chemotherapy. Thus, magnetic nanoparticles are recurrently used for both diagnosis and therapeutic applications in cancer treatment [1].

Although these techniques are discovered decades back, developments and researches in this field are still growing very faster. There are many reasons behind this. For cancer treatment, magnetic nanoparticles aid in both diagnosis and therapy [2]. Both diagnostic applications as well as therapeutic applications are equally

S. Balachandran (✉)
Department of Zoology, Sacred Heart College, Kochi, Kerala 682013, India

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important for the treatment of cancer ailments. The greater fenestrated vasculature and poor lymphatic leakage enable greater mNP uptake by tumour cells. This is called enhanced permeation and retention effects (EPR) of mNPs [3–5]. Thus, EPR is an interesting factor that makes mNPs a better candidate for cancer therapies.

Major roles of mNPs in cancer:

(1) Imaging
(2) Therapy

2 Factors Affecting MNPs Inside Living System

Living beings are highly complex systems, and therefore, incorporating external substances to this complex system requires considerations about various regulating factors. Living system is protected with highly active immune system, and so, the administration of mNPs must not awake immune responses. So, acute care must be provided while choosing the apt mNPs. Some of the most important factors to be considered are enlisted below:

(1) **Charge**
Positively charged magnetic nanoparticles tend to get more internalised than negatively charged ones [6–8]. The reason behind this is so simple, i.e. negatively charged outer surface of cell membrane always favours internalisation of positively charged particles [9, 10]. Liver usually eliminates the negatively charged ones [8]. During endocytosis of nanoparticles, rejection of negatively charged nanoparticles by cell membrane occurs very easily. Neutrally charged particles exhibited profound results showing maximum half life [10].

(2) **Size**
Particles below 10 nm can easily be eliminated from blood during renal excretion, thus reducing their half-life in blood [11, 12]. Mononuclear phagocyte system (MPS) eliminates the large-sized nanoparticles. So, particle size of nanoparticles is suggested to range between 10 and 200 [13–15].

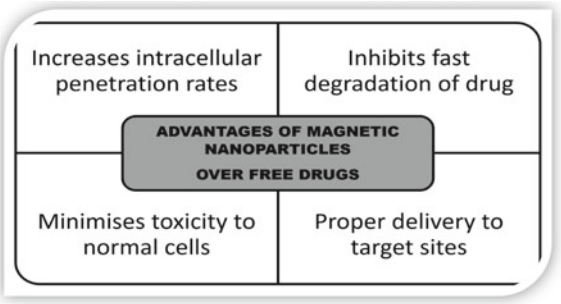

Fig. 1 Advantages of magnetic nanoparicles over free drugs

(3) **Shape**
A clear idea about the relevance of shape of magnetic nanoparticles is clearly unknown. It is suggested that for targeted therapies, rod-like or disk-like structures are more efficient when compared with spherical structures with same combinations [8].

(4) **Toxicity**
Cellular concentration on materials used for the preparation of magnetic nanoparticle might also be clearly considered. If higher concentration than the normal recommended levels are present, they can result in cytotoxicity [1]. For example, iron concentration above 60 mg/kg body weight is toxic for humans.

(5) **Protein Adsorption Capacity**
Nanoparticles interact with plasma proteins immediately after intravenous injection. The adsorption of proteins is greatly depended on size, charge and hydrophobicity of nanoparticle. Protein adsorption capacity increases with the increase of size, charge and hydrophobicity of nanoparticle [16] (Fig. 2).

3 Magnetic Nanoparticles for Cancer Imaging

The first and foremost aim as of any other treatment is to diagnose the disease. Importantly, imaging techniques play a key role in these diagnoses. Imaging helps to easily distinguish between normal and abnormal cells at their physiological environment itself. The selection of imaging techniques depends on the symptoms, organs, age, health status of patient, etc. A very few of the practising imaging techniques are as follows:

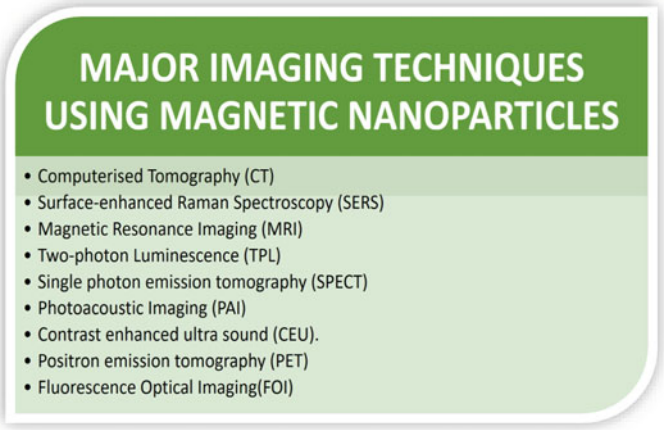

Fig. 2 Major imaging techniques using magnetic nanoparticles

3.1 Magnetic Resonance Imaging

There are many available imaging techniques with unique properties including computed tomography (CT), magnetic resonance imaging (MRI), ultrasound (US), positron emission tomography (PET) and so on. Out of these techniques, magnetic resonance imaging is one of the routinely and most extensively used non-invasive techniques for imaging. It is highly important because it uses radio waves for imaging and further leaves minimum complexities to the living system. It is the most frequently used technique for imaging of the brain, heart, cartilage blood vessels, tumour detection and so on.

Magnetic resonance imaging is having an added advantage during the usage of mNPs for the personalised treatment with individual concerns [17]. Paramagnetic properties of mNPs enable it easier to act as contrast agents during imaging [18]. Iron oxide NPs with magnetic properties are considered to be the best candidates for MRI imaging. The major reason behind this is that they can exhibit superparamagnetism [19]. Superparamagnetism enables a candidate to exhibit magnetic properties only when provided with an external magnetic field. They can revert these properties in the absence of the externally provided magnetic field. Magnetic resonance imaging scanners cannot directly detect these mNPs, indeed they induce contrast improvement effects on the magnetic resonance images, either as a signal increasing or decreasing contrast agent [20].

Although many kinds of MRI contrast agents are used, they can be broadly grouped into three on the basis of the mechanisms used for generating contrast images. Those agents that can produce positive contrast by shortening the longitudinal relaxation time of water molecules that are present in their surroundings are referred to as T_1, whereas T_2 agents usually generate contrast images by shortening the transverse relaxation time of surrounding water protons. The final group adopts chemical exchange saturation transfer (CEST) mechanism for acting as a good contrast agent and is the relatively the latest approach to enhance MRI contrast [21]. The major platforms used for the preparation of CEST probes include liposomes, micelles, apoferritin, mesoporous silica, etc.

Approval of mNPs for MRI was done in 1990 by Food and Drug Administration (FDA) [22]. Gadolinium-based compounds are the most commonly used inorganic compound that can be very effectively used as contrast agents for magnetic resonance imaging [23]. They are found to exhibit long circulation time in the body fluid. They can be very easily conjugated with other biomolecules. These can also be used for therapeutic applications beyond imaging. Following gadolinium, manganese-based inorganic compounds are also recurrently used as contrast agents. These manganese-based inorganic compounds are found to exhibit good biocompatibility as well as low toxicity. Ultra-small iron oxide nanoparticles are also seen to be utilised effectively as contrast agents. These compounds are highly effective due their supermagnetic properties. Dysprosium and holmium are also promising candidates for MRI in an ultra-high magnetic field and due to large magnetic moment and short electronic relaxation time [23].

Surface properties of mNPs are another important factor that may contribute for acting as a contrast agent. This is mainly depended on the interaction between NPs and water molecules. To increase the contrast effects, coating materials such as organic surface ligands (e.g. mercaptosuccinic acid), an inorganic nanolayer (e.g. Fe_2O_3, Fe_3O_4, $NaGdF_4$,) or mesoporous silica shells are very commonly used. Beyond the size and surface properties, shape of NPs can also affect the imaging. It was suggested that iron oxide nanorods exhibited lower magnetisation than spherical iron oxide NPs having the same volume [24].

Advantages of MRI

- A great spatial contemporary resolution [25]
- Use of non-ionising radiation
- High-imaging resolution,
- 3D-imaging capability
- Detection of anatomical information in soft tissues (after drug delivery).

Advantages of NPs for MRI

- High contrast imaging at minimum dose of contrast agent
- Low cytotoxicity relating with contrast agent
- Large surface area of NPs offers improved reactivity
- Ability to bind with other surface moieties to improve targeting.

3.2 Positron Emission Tomography

PET enables us to visualise and monitor various biological/physiological phenomena using radiolabelled probes in the living systems. mNPs are found to be interesting candidates for PET imaging when they are conjugated with suitable radio nucleotides. Various radioisotopes including Nitrogen-13 (^{13}N), Iodine-124 (^{124}I), Iron-18 (^{18}F), Gallium-68 (^{68}Ga), Carbon-11 (^{11}C), Copper-64 (^{64}Cu), Yttrium-86 (^{86}Y), Oxygen-15 (^{15}O), etc., are used for this imaging technique. Here, results are estimated according to the amount of γ rays emitted by the radioisotopes [26].

3.3 Single Photon Emission Computed Tomography

SPECT is an attractive technique using radiolabelled isotopes for imaging of numerous endogenous ligands. Controlled delivery and release of drugs can easily be achieved through the combination of mNPs with SPECT radioisotopes [26]. The commonly used radioisotopes for SPECT imaging include Indium-111 (^{111}In),

Gallium-67 (^{67}Ga), Iodine-123 (^{123}I), Iodine-131 (^{131}I), Rhenium-186 (^{186}Re), Rhenium-188 (^{188}Re), Copper-67 (^{67}Cu), Lutetium-177 (^{177}Lu), etc.

4 Magnetic Nanoparticles for Cancer Therapy

The primary aim, as in any other kind of treatment procedures, was to detect (diagnose) whether any kinds of tumours is present in the living system. After diagnosis, proper measures are to be taken so as to limit further growth and proliferation of the diagnosed tumour. Thus, the main aim in administration of mNPs is the eradication of the tumour cells from the living system. Here, we discuss briefly about the various therapeutic applications that can be done using mNPs.

4.1 Magnetic Nanoparticles for Hyperthermia

Hyperthermia is commonly used therapeutic approach where a particularly targeted region is subjected to a temperature exceeding the normal physiological temperature, which might lead to its distrust the targeted area [27]. Radiofrequency waves, ultra sounds or even microwaves are usually used in conventional hyperthermia treatment. Here, the mNPs are targeted to cells using various other techniques, and further, an alternating magnetic field (AMF) is given to generate temperature inside cells [28]. Usually, the heat generated may vary accordingly and might range within 41–46 °C. The success rate of magnetic hyperthermia depends on the specific absorption rate (SAR) of mNPs used. SAR is the ability of a substance to produce heat under an externally provided alternating current (AC) magnetic field. In some cases, "thermoabalation" may take place when temperature might raise up to 56 °C, resulting in necrosis, carbonisation or coagulation of the administrated tissue [29]. The quality of hyperthermia can be clearly evaluated based on the duration of treatment and amount of temperature produced. Since health concerns are growing day by day, novel therapies are highly welcomed. In these kinds of situations, nano-based products are highly relevant [30]. Magnetic nanoparticle-mediated hyperthermia for cancer ailment is yet another innovation in the field of nanotechnology. This method for cancer treatment exhibited profound results for tumour healing without leaving any kinds of serious side effects [31].

The major component controlling hyperthermia is the controlled heat generation. It is governed by both intrinsic and extrinsic factors. The major extrinsic parameters to be considered for controlled heat generation during magnetic hyperthermia include amplitude and frequency of the generated magnetic field and viscosity of the surrounding fluid media. Major intrinsic parameters to be considered for controlled heat generation during magnetic hyperthermia include the size of nanoparticles, anisotropy, concentration or collective behaviour of NPs, etc.

Physiological factors and host factors are also equally responsible for the cellular responses induced as a result of hypothermia [32]. So, new strategies were introduced to increase the efficiency of hyperthermia. Combining radiotherapy along with hyperthermia gives profound advantages in cancer therapies [33, 34]. Evidences reveal that curing rates for patients with hyperthermia or radiation are very less when compared with the combination of hyperthermia with radiotherapy [35]. Complete response (complete curing) was reported in mice due to administration of iron oxide nanoparticles combined with radiotherapy [34]. This is due to the ability of ionising radiations to cause DNA damage is further added upon by hyperthermia by halting DNA repair mechanism [36]. One of the best such studies was reported when human patients were treated for brain and prostate tumours [37]. NPs conjugated to antibodies against surface receptors which can specifically target cell membrane can easily damage membrane without affecting its environment by inducing hyperthermia [38]. Iron oxide NPs with magnetic properties are considered to be one of the best candidates for magnetic hyperthermia since they exhibit superparamagnetism [39]. Superparamagnetism enables a candidate to exhibit magnetic properties in the presence of an external magnetic field whereas reverting its properties in its absence.

It was in 1900s, the idea about the direct administration of mNP into the tumours for their treatment was put forward for the first time [40]. One of the pioneer reports about the therapeutic application of hyperthermia was published in 1957 for treatment of lymphatic metastasis using magnetic nanoparticles. An alternating magnetic field (AMF) was produced following the administration of magnetic nanoparticles for producing such conditions [41]. Magnetic nanoparticles can also be directly injected to the cancerous cells, enabling it to get retained in the tumour site for longer durations [42]. The first clinical study using the magnetic nanoparticles-mediated hyperthermia was done to treat prostate cancer in a 67-year-old patient in 2005 [43]. Location of nanoparticles administration is also very important, i.e. intracellularly administrated nanoparticles exhibit more efficiency in inducing hyperthermia when compared with interstitial or membrane bound [29].

Hyperthermia is classified depending on the location where its application is targeted:

(1) *Local hyperthermia* (LHT) is employed to treat superficial tumours. It is the most commonly preferred type due to its high specificity. The major aim is to increase the temperature of the tumour. Both external as well as interstitial methods are employed to induce LHT. Specific antennas or applicators emit radio waves or microwaves which help in heating up of the targeted surface having a contacting media. The area that can be heated strictly depends on the type of applicator used for generating energy and the physical characteristics of the energy source.

- *External hyperthermia* refers to the simplest form of hyperthermia, usually employed to treat tumours below the skin. The antennas or applicators are placed near the targeted site, and temperature is generated for the treatment of tumours.
- *Endocavity hyperthermia* mainly focuses treatment of tumours that are seated within body cavities and natural openings. This is done by inserting specialised antennas through natural opening of hollow organs. It is also called intraluminal hyperthermia.
- *Interstitial hyperthermia* is a type of LHT, suitable to treat tumours which are deep seated and that are less than a diameter of 5 cm. Usually, antennas are implanted within the tumours. This technique is usually employed under anaesthesia [35, 44] (Fig. 3).

(2) *Regional hyperthermia* (RHT) is performed with the help of multiple heating applicators around the targeted body part. This is usually done to eliminate large number of tissues, for example, deep-seated tumours like that of pelvis or abdomen. The amount of temperature to be generated is controlled by optimising the number of applicators along with their amplitude and phase.

- *Deep tissue hyperthermia* approaches are mainly used in targeting cancer cells within the body like cervical cancer. The external applicators used in generating hyperthermia are placed around the body part to be treated, following the application of microwaves or radio waves.
- *Regional perfusion hyperthermia* is a type of RHT usually applied to treat melanomas in arms and legs. The blood supply to the specific body part is separated from rest of the body part, this blood is pumped out to specific heating devices, and further, this is pumped back. Chemotherapeutics are usually administrated along with this treatment.

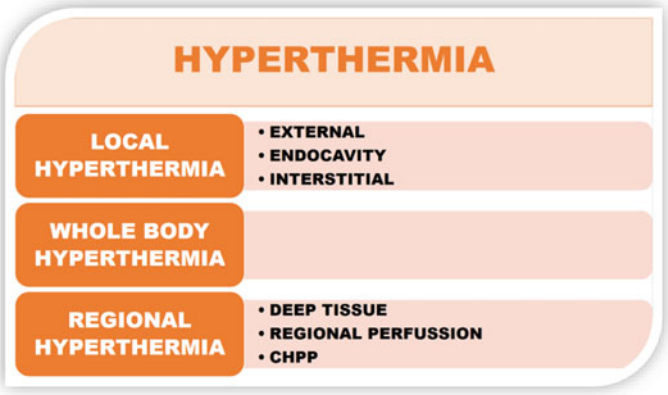

Fig. 3 Hyperthermia

- *Continuous hyperthermic* peritoneal perfusion (CHPP) is another type of RHT, usually used in treatment of cancer within the peritoneal cavity. Here, heated anticancer drugs are passed through the target are from the heating device, following surgery in the affected body part. This is a type of hyperthermia therapy (Fig. 4).

(3) *Whole body hyperthermia* (WBH) can be achieved with the help of highly specialised Aquatherm radiant heating devices. The procedures used for achieving WBH vary. This method is usually adopted when the carcinoma exhibits distant metastasis. These procedures are usually done under anaesthesia. The temperature is usually controlled between 40 and 42 °C. The feasible time estimated is 6 h. Cytotoxic drugs and cytokines combined with WBH are found to exhibit better therapeutic index. Systemic chemotherapy combined with WBH exhibits promising effects for patients with metastatic malignancies. Several sarcomas and ovarian cancers were treated effectively when WBH is combined with chemotherapy.

4.2 Magnetic Nanoparticles for Radiotherapy

Out of the various conventional treatments adopted for the treatment of cancer, radiotherapy had been practised for the last few decades. Radiotherapy uses greater doses of ionisation radiation that helps in killing cancer cells, thus inhibiting the progression of cancer. mNPs enables proper targeting of chemotherapeutic drugs to the target site. The most commonly used among them is the supermagnetic iron oxide nanoparticles, which are highly biocompatible. The major advantage of using mNPs in comparison with that of conventional radiotherapy is that they increase the

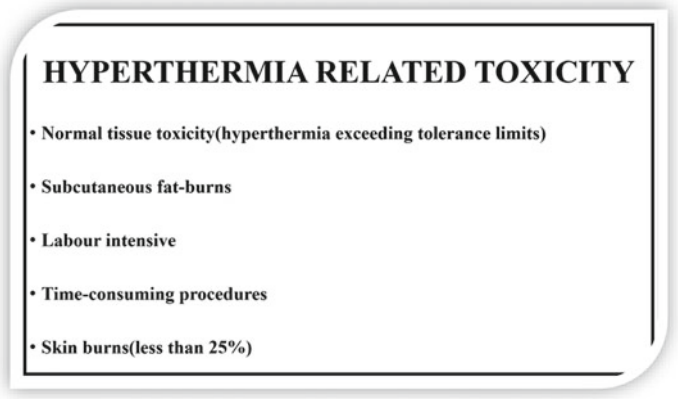

Fig. 4 Hyperthermia related toxicity

targeting specificity. Another interesting application is that a static magnetic field can be easily generated after administration of radioisotope tagged mNPs. This enables to induce the profound advantage of hyperthermia, as explained in the earlier session. Commonly used radioisotopes for radiotherapy are depicted in Fig. 5 [45].

Adverse systemic toxicity is the major limitation for using conventional anti-cancer drugs, since they cannot efficiently differentiate between normal cell and cancerous cells. Monoclonal antibodies eliminate this non-specific targeting of chemotherapeutics. This is achieved by correctly recognising a specific cell surface marker in cancer cells and further constructing specific monoclonal antibodies against these specific cell surface markers. This identification helps in specifically targeting cancer cells and thus reducing the side effects of conventional radiation therapy. This kind of treatment for systemic radiation is commonly called as radioimmunotherapy.

4.3 Magnetic Nanoparticles for Phototherapy

Phototherapy is a non-invasive method which uses phototherapeutic agents in combination with radiations to specifically target and kill cancerous cells so that the nearby cells are minimally affected [46]. It includes both photothermal therapy (PTT), which uses near-infrared laser irradiations to generate heat which leads to the thermal ablation of cells [47] and photodynamic therapy (PDT), which uses photosensitizers to produce certain cytotoxic reactive oxygen species [48] to kill cells [49]. In PTT, laser beams are used to illuminate targeted tumour cells, and further, these radiations are transformed into heat using a light absorbing material [50]. As the light absorbing efficiency of the photothermal agent increases, the better will be the results of PTT.

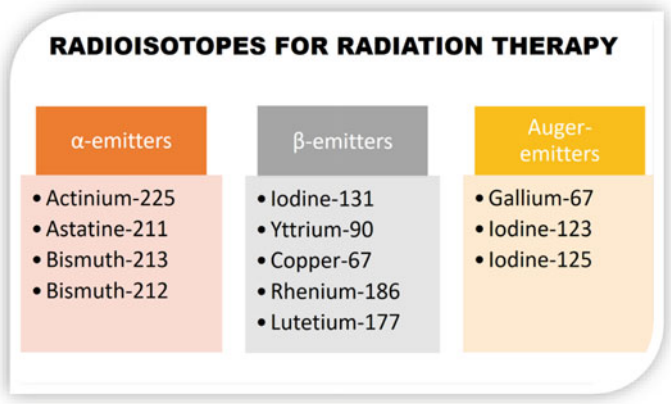

Fig. 5 Radioisotopes for radiation therapy

Characteristics of good photothermal agents include [51]

- Maximal biocompatibility and minimal toxicity
- Enhanced accumulation in tumour cells
- Ability to absorb NIR radiations
- Greater absorption cross section to maximise light to heat conversion.

Both organic as well as inorganic materials are used as candidates for photothermal agent. But, organic compounds were found more attractive when compared with inorganic ones [52]. The main reason behind this attractiveness is the escape from immune system. Out the numerous compounds available for the production of photothermal agents, iron oxide nanoparticles are found to be the more attractive due to biodegradability, low toxicity, facile synthesis, biocompatibility, etc. [52, 53] (Table 1).

The major problems faced during phototherapy include

- Production of immune responses against nanoparticles [65]
- Mononuclear phagocyte system picks and clears nanoparticles from circulation [66]
- Improper delivery of nanoparticles to their target sites [67].

To escape from above-mentioned problems, which might lead to failure of phototherapy, membrane coating approaches or membrane camouflaging approaches are usually equipped [2].

Some of the most commonly used approaches are as follows:

- Coating with normal cell membrane
- Coating with erythrocyte cell membrane
- Coating with platelet cell membrane
- Coating with cancer cell membrane
- Coating with macrophage cell membrane
- Coating with stem cell membrane
- Coating with fibroblast cell membrane.

Table 1 Common organic compounds used for PTT

Sl. No.	Compound	Reference
1	Copper sulphide	[54]
2	Graphene oxides	[55, 56]
3	Manganese	[57]
4	Manganese and graphene oxide	[58]
5	Molybdenum sulfide	[59, 60]
6	Prussian blue	[61, 62]
7	Copper/selenium	[63, 64]

5 Magnetic Nanoparticles for Drug Delivery

Magnetic nanoparticles are widely used for the targeting and the proper delivery of chemotherapeutics [30]. Different synthesis methods must be followed to rationalise proper targeting. Numerous factors must be considered during the synthesis process [68]. Based on the differences in the properties of chemotherapeutic drug used, either the drug can be conjugated to the surface-active groups of NPs or can be encapsulated with NPs. Major objectives to be taken under consideration during the development of mNP and related drug delivery system include reduction in side effects contributed by the cytotoxicity of the drug and to minimise drug dosage to optimise maximum results [69]. Specific coating to the mNP is found to be more effective in proper targeting [70]. Although drug-loaded magnetic nanoparticles are widely used for the chemotherapeutic loading and targeted cancer therapy, antimicrobial drugs, proteins, genes, etc., can also be targeted through NP [71].

Promising reports about doxorubicin coated with magnetic nanoparticles to treat liver cancer were clearly elucidated in in vivo models [72]. Remission of tumour was effectively done, while magnetic iron oxide NPs was bounded with anthracendion derivative MTX-HCL [73]. Anthracendion derivative MTX-HCL is a strong intercalating agent inhibiting nucleic acid synthesis. Various evidence shows that Insulin like Growth Factor 1Receptor (IGF-1R) is highly expressed in numerous drug-resistant tumour cells [74]. So, recombinant human IGF1 is used as one of the best targeting ligands to be conjugated with iron oxide NPs carrying doxorubicin. Effectiveness of these targeted iron oxide NPs was evaluated in a human pancreatic cancer patient tissue-derived xenograft model giving positive results.

The most commonly used approach for the designing of drug delivery includes the usage of biopolymers as coating substrates. The most commonly used such biopolymers include Chitosane derivatives, dextran and hyaluronic acid. The major reason behind this is that they exhibit better biocompatibility [75]. Development of different artificial biocompatible polymers is also seen as an upcoming revolutionary change in this field. Polyethylene-glycol copolymers and Pluronic P85 block copolymer are some of the other attractive candidates among them.

Beyond the drug coating mechanisms for drug delivery, it is also important that how is the drug delivery mechanism taking place. Tumour microenvironment provides different kinds of specificities for the drug delivery. Since all tumour cells are having slightly acidic pH, we usually adopt this mechanism for the drug release. Another such mechanism involves detection of adenosine triphosphate (ATP), which is usually upregulated in tumour cells. In some cases, external stimuli are also used for drug release. These include the use of infrared radiations and external electrical forces. A very novel drug delivery system includes the controlled drug release. Mesoporous silica nanoparticles are the commonly used for the preparation of these control release drugs. These are more advantageous because they help to retain drugs for a long time without the help of persistent drug administration (Table 2).

Table 2 Different types of targeting agents for cancer therapy

Sl. No.	Target	Examples
1	Proteins	Rituxan, Herceptin, Avastin
2	Nucleic acid	Aptamer
3	Receptor ligands	Heparin sulphate, Hyaluronan, Chondroitin sulphate

6 Challenges in Drug Delivery

Multiple drug-resistant (MDR) transporters are the major challenging candidates in drug delivery systems [4]. These transporters pump out chemotherapeutic drugs and maintain intracellular drug levels below dangerous threshold. Combinatorial treatment of nanoparticles along with MDR pump would probably help in proper treatment.

7 Conclusion

We have discussed briefly about a very novel strategy in the field of life sciences. This has helped in combining the application of nanomaterials in the field of diagnosis and treatment of cancer. Different individual approaches and combination multimodal approach were described briefly to convey about the effectiveness of the treatment using magnetic nanoparticles. There is yet more research needed to produce better results and higher survival rates in clinical trials. We hope this treatment strategy will be highly helpful for oncologist in the treatment of cancer. In the coming future, the fear of cancer as a drastic incurable disease can be completely removed from the society with application of new strategies like this.

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