Chapter 2
Biomedical Applications of Functionalized Magnetic Nanomaterials (FMNs)

Murali Mohan Achari Kamsali and Vasantha Thoti

Abstract Over the past few decades, nanomaterials have been extensively used in various fields, especially in biomedicine and healthcare. Their unique physicochemical properties, such as high surface area and nanoscale size, make them highly desirable. Recently, there has been significant interest in developing therapies based on magnetic nanoparticles for biomedical applications, owing to their unique advantages. Magnetic particles, which respond to magnetic forces, are useful in drug targeting and bioseparation, including cell sorting. To be used in biomedicine, these magnetic nanomaterials often need to be modified or functionalized with other materials. This functionalization allows them to be used in various biomedical applications, such as biosensing, drug delivery, imaging, medical implants, cancer treatment, antibacterial and antiviral applications, and tissue engineering. Additionally, functionalized magnetic nanomaterials (FMNs) have applications in hyperthermic treatments. For instance, magnetite nanoparticles conjugated with antibodies, known as antibody-conjugated magneto-liposomes (AMLs), are used in hyperthermia and enhance tumor-specific contrast in MRI via systemic administration. This chapter provides a critical overview of recent research on functionalized magnetic nanomaterials in biomedical applications. It also discusses the role of the magnetic properties of these nanomaterials in targeted therapeutic approaches and improved diagnostic tools.

Keywords Biomedicine · Functionalized magnetic nanomaterials (FMNs) · Drug delivery · Tissue engineering · Hyperthermia · Applications

M. M. A. Kamsali (✉) · V. Thoti
Department of Chemistry, Sri Venkateswara College, University of Delhi, Delhi, India
e-mail: mmakamsali@svc.ac.in

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2.1 Introduction

Functionalized magnetic nanomaterials (FMNs) are an evolving area in nanotechnology aimed at enhancing the properties and functionalities of nanoscale materials through modification. These materials, typically between 1 and 100 nm, possess unique physical, chemical, and biological traits due to quantum confinement effects and high surface area-to-volume ratios. Nanomaterials (NMs) with at least one dimension in the nanoscale range exhibit novel properties such as improved mechanical strength, electrical conductivity, and catalytic activity, making them valuable in medicine, electronics, and environmental science. Functionalization, which involves attaching various functional groups, molecules, or coatings to the surface of nanoparticles (NPs), tailors their properties for specific uses, enhancing compatibility, reactivity, and stability for diverse applications [1]. This process allows NMs to interact more effectively with biological systems, electronic devices, or environmental contexts.

FMNs are notable due to their high stability, large magnetic moments, and excellent response to moderate magnetic fields. Their unique properties enable them to cross biological barriers, protect drugs from rapid degradation, and provide a large surface area for conjugating targeting ligands. Additionally, FMNs offer low production costs and superparamagnetism for external magnetic field-guided targeting. Over the past decade, research on FMNs has surged, particularly in high-interest biomedical fields such as biomaterial science, diagnostics, magnetic drug and gene delivery, hyperthermia, magnetic resonance imaging (MRI), and theranostics. FMNs have shown utility in drug delivery, medical imaging, and tissue engineering. Magnetic nanoparticles, for instance, have been extensively studied for targeted drug delivery and hyperthermia treatment in cancer therapy. Cancer remains a major global health issue, responsible for one out of every eight deaths worldwide. The International Agency for Research on Cancer (IARC) projects approximately 13.1 million cancer-related deaths by 2030 [2]. The rise in cancer cases is attributed to genetic predisposition, immune deficiencies, industrialization, population growth, and lifestyle changes. Current trends suggest a potential 70% increase in cancer cases, necessitating innovative therapeutic approaches. Magnetic nanoparticle-mediated hyperthermia has emerged as a promising cancer treatment modality, utilizing the heat-generating properties of superparamagnetic iron oxide nanoparticles (SPIONs) under an alternating magnetic field. Hyperthermia raises tissue temperatures to 40–45 °C, leading to cancer cell destruction or growth inhibition. Studies show that hyperthermia synergistically enhances radiotherapy and chemotherapy, offering a promising strategy to improve cancer treatment outcomes.

Beyond cancer therapy, FMNs are significant in cell therapy, tissue engineering, and regenerative medicine by modulating stem cell functions. Functionalized nanoparticles can be modified with bioactive molecules to serve as vehicles for drug or gene transport, aiding in controlled stem cell differentiation and regeneration under magnetic field influence. They can also be incorporated into biocompatible scaffolds with cells or bioactive substances to support tissue regeneration.

Developing diverse scaffold materials with optimized surface properties has been crucial in biomedical research to promote cell adhesion and proliferation for specific applications. Among the promising nanoscale materials are iron oxide nanoparticles (IONPs), which can be functionalized with bioactive substances, embedded in composites, and internalized by cells. IONPs are widely used in drug delivery systems for targeted delivery through specific binding proteins like antibodies or external magnetic fields. Additionally, primary cells and cell lines can be magnetically labeled with IONPs, facilitating non-invasive in vivo monitoring of cell therapy efficacy using MRI [3].

Apart from biomedical applications, FMNs have extensive utility in environmental remediation, including water purification, pollutant degradation, and air filtration. Functionalizing nanoparticles with catalytic or adsorptive properties effectively removes contaminants from water and air, contributing to environmental sustainability. In energy storage, FMNs improve the performance of batteries, supercapacitors, and fuel cells due to their superior electrical conductivity, chemical stability, and surface area, enhancing efficiency and longevity. FMNs also have potential in electronics, with applications in sensors, transistors, flexible electronics, and photodetectors. By tailoring the electronic and optical properties of nanomaterials, researchers develop devices with enhanced performance and novel functionalities [4].

This chapter focuses on the biomedical applications of FMNs, focusing on their roles in drug delivery, imaging, and tissue engineering. It highlights recent advancements and future prospects, emphasizing how the magnetic properties of FMNs enable targeted therapeutic approaches and improve diagnostic tools.

2.2 Functionalized Magnetic Nanomaterials (FMNs) in Drug Delivery

2.2.1 Targeted Drug Delivery

Functionalized nanomaterials (FMNs) have revolutionized drug delivery systems by enhancing precision and effectiveness through their magnetic properties. Advanced research has developed multicomponent nanoparticles that combine magnetic and other functional elements, enabling combination therapies targeting multiple disease pathways. These nanoparticles, known as magnetic targeted carriers, deliver particles precisely to target tissues. Surface coatings on these particles improve medicinal properties, preventing pharmacokinetic effects and toxicity from cell or protein interactions, thus enhancing biocompatibility. Functionalizing nanoparticles with ligands or antibodies ensures accurate targeting, reducing harm to healthy tissues. This targeted approach has shown benefits in cancer therapy, with folic acid-functionalized nanoparticles effectively targeting cancer cells. Additionally, nanoparticles functionalized with chemotherapeutic drugs and RNA molecules have increased treatment efficiency and reduced side effects [5]. Their size, remote control capability,

and resonance response to magnetic fields make magnetic nanoparticles valuable in biomedicine.

2.2.2 Classification of Magnetic Nanoparticles

To select the most suitable magnetic nanoparticles (MNPs) for specific biomedical applications, it is essential to clearly classify them based on their nature, composition, and size, considering the synthesis methods and surface functionalization. Several types of MNPs have been developed and researched over time. Generally, these MNPs are grouped into three main categories: (i) Magnetic pure metals (Fe, Co, Ni), (ii) Magnetic metal oxides (Fe_2O_3, Fe_3O_4) or ferrites (MFe_2O_4, where M = Fe, Co, Zn), (iii) Multicomponent magnetic nanoparticles as core/shell MNPs or magnetic nanoclusters (Fig. 2.1). Each category has advantages and disadvantages, but its properties can be tailored for specific applications. The following sections will discuss and exemplify each category.

2.2.2.1 Magnetic Pure Metals

Pure metal materials possess distinctive properties shaped by electron distribution, particularly their magnetic behavior. Transition metals such as Fe, Ni, Co, and Mn are frequently utilized for their exceptional magnetic performance in biomedical applications. Iron nanoparticles are extensively employed due to their superior magnetic properties. Although cobalt has higher toxicity, it is also used in MRI imaging and hyperthermia treatments for tumors [6].

2.2.2.2 Magnetic Metal Oxides

Iron oxide is distinguished by its excellent magnetic properties and lower toxicity, making it ideal for nanotechnology applications. Metal oxides are preferred in biomedical fields due to their stability, low toxicity, and biocompatibility, particularly for magnetic bio-separation, hyperthermia, targeted drug delivery, and biosensing. Coating iron oxide nanoparticles (NPs) with biocompatible layers improves stability and reduces toxicity. Superparamagnetic iron oxide nanoparticles (SPIONs), 10–30 nm in diameter, are beneficial for controlled drug delivery under an external magnetic field. Spinel ferrites ($MeFe_2O_4$), doped with divalent transition metals, are tailored for specific biomedical applications, combining electrical and magnetic properties. Coated ferrite NPs with stabilizing molecules like PEG ensure biocompatibility and safe drug release without adverse toxicity effects [7].

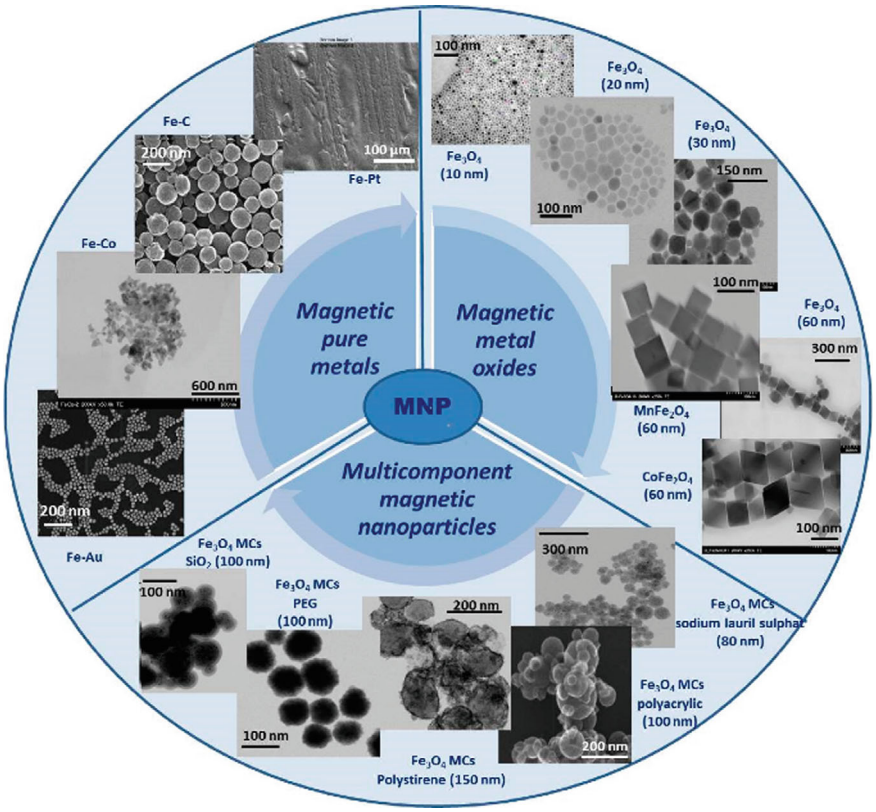

Fig. 2.1 Categorization of magnetic nanomaterials (All images are original and credited to the authors) Ref. [7] © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open-access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY-4.0) license (https://creativecommons.org/licenses/by/4.0/)

2.2.3 Multicomponent Magnetic Nanoparticles

Multicomponent MNPs have evolved to offer multiple functionalities by combining two or more components, providing new features unavailable in single-component materials. The two main categories of multicomponent magnetic structures with potential biomedical applications are:

2.2.3.1 Core/Shell-Type MNPs

These are the most common and widely studied multicomponent nanoparticles. Initially used in semiconductors to modify electrical and optical properties, the concept was extended to magnetic systems to protect and enhance metallic MNP

properties, especially reactive Fe nanoparticles. Some core/shell magnetic systems feature a bimagnetic core, combining two magnetic metallic species covered with an oxide layer. Examples include FePt/Fe_3O_4, FePt/ZnO, Fe_3O_4/ZnO, and Fe_3O_4/Au, which benefit from the SPION core's magnetic properties and the noble metals' plasmon resonance properties [8].

2.2.3.2 Magnetic Clusters (MCs)

These are created by the controlled self-assembly of superparamagnetic nanoparticles into three-dimensional clusters. MCs have gained popularity in biomedical applications due to their innovative collective properties. Depending on the preparation method and the nature of functionalizing polymers, MNPs can form clusters of various shapes and sizes, such as spheres, rods, and nanorings. MCs with a polymer coating show promise for theragnostic applications, enhancing MRI and hyperthermia performance and allowing for the encapsulation and targeted release of drugs [9].

2.2.4 Limitations and Solutions to Overcome These Limitations in the Use of MNPs in Biomedical Applications

For effective biomedical applications, identifying ideal properties for the functionalization of bio-MNPs is crucial to enhance performance. Key factors include colloidal stability in aqueous environments to prevent agglomeration and potential negative effects on human health and the environment. Proper surface functionalization ensures biocompatibility and biospecificity. Research focuses on surface modifications to improve colloidal stability, prevent aggregation, ensure non-toxicity in physiological conditions, and introduce functional groups for targeting specific molecules. MNPs must have low toxicity and high biocompatibility for biomedical applications. MNPs can generate reactive oxygen species that cause cellular-level toxicity, including mitochondrial destruction and DNA damage. Factors like shape, size, and surface properties affect biocompatibility. Enhancing biocompatibility involves functionalizing MNPs with agents like polymers, proteins, or inorganic compounds. Proteins like albumin and silica coatings improve biocompatibility, and noble metal coatings, such as gold, further reduce toxicity [10].

2.3 Functionalized Magnetic Nanomaterials (FMNs)—Magnetic Resonance Imaging (MRI) and Diagnostics

MRI is a widely used non-invasive diagnostic technique in medicine for generating detailed images of soft tissues. When a magnetic field (B_0) is applied, hydrogen protons align with the field. MRI measures the net magnetization (M) of these protons. A radiofrequency pulse disrupts M_0 (equilibrium magnetization), causing it to spin out of equilibrium. Upon stopping the pulse, M returns to equilibrium through relaxation. This process creates detailed images. There are two relaxation processes: longitudinal (T1—recovery) and transverse (T2—decay). T1 relaxation involves energy exchange with the surroundings, producing bright signals (positive contrast). T2 relaxation involves energy transfer between spins, creating dark signals (negative contrast). T2* is an apparent transverse relaxation time affected by magnetic field inhomogeneities, making it shorter than T2. MRI can differentiate between ischemic and hemorrhagic strokes, assess damaged areas, locate metastasis, determine tumor size and stage, and diagnose demyelinating diseases, Alzheimer's dementia, and congenital heart diseases [11].

2.3.1 Overcoming MRI Limitations with FMNs

MRI's drawbacks include low specificity and high cost compared to other imaging methods like CT. This is particularly evident in breast cancer screening, where MRI's expense limits its use to high-risk groups and difficult-to-detect lesions. Consequently, professionals often prefer cheaper, faster tests such as ultrasound and mammography. Additionally, MRI's low specificity can lead to false positives and unnecessary treatments. FMNs offer a solution by enhancing MRI sensitivity and specificity, as they accumulate in target tissues, shortening proton relaxation times and improving MR images. Some FMNs shorten both T1 and T2 relaxation times, leading to dual-mode T1- and T2-weighted MRI for increased diagnostic accuracy. Dual-mode imaging produces matching T1- and T2-weighted images using a single system, providing complementary information for a more complete diagnosis. Dual-mode agents can be created through metal doping of IONPs or synthesizing MNPs with a T2-weighted core and T1-weighted shell, potentially enhancing MRI's diagnostic accuracy. MNPs can also serve as multimodal imaging platforms, such as PET-MRI, combining PET's high sensitivity with MRI's high resolution for a comprehensive examination. Many FMN formulations have completed clinical trials and received approval as MRI contrast agents [12].

2.3.2 IONPs' Clinical Uses

Numerous iron oxide nanoparticle (IONP) formulations have been approved for clinical use by the EMA and FDA, such as ferumoxytol, ferumoxide, ferumoxsil, and ferristene. Ferucarbotran and Sienna+® are approved in the EU but not in the USA. Ferumoxytol is user-friendly, administered as an IV bolus for MRA and dynamic MR, and treats IDA in adults with CKD. Ferumoxide enhances T2-weighted MRI for liver lesion detection. Ferumoxsil and ferristene are used orally for gastrointestinal imaging. Ferucarbotran is an IV liver imaging contrast agent in Germany. Sienna+® is used for sentinel lymph node detection in breast cancer. Ferumoxtran is researched for CNS visualization and MRI contrast enhancement in MS patients. Feruglose is used for coronary angiography. Mn-based agents like Mangafodipir and LumenHance™ were approved for liver imaging but withdrawn due to toxicity concerns. Mn_xO_y nanoparticles are promising for T1-weighted MRI with better toxicity profiles than Gd-based agents. Holmium (Ho) nanoparticles show significant potential in ultra-high MRI and are non-toxic at low concentrations. These advancements highlight the diverse and promising applications of IONPs in clinical imaging and diagnostics. Ni et al. reported r2 relaxation values of 222.6 mM^{-1} s^{-1} at 7 T for $NaHoF_4$ nanoparticles, whereas Atabaev et al. created PEGylated Ho_2O_3 nanoparticles with an r2 of 23.47 mM^{-1} s^{-1} at 1.5 T and green fluorescence resulting from intra-4f-transitions in Ho ions. Cytotoxicity studies showed these PEG-Ho_2O_3 nanoparticles were non-toxic at concentrations below 16 μg/mL [13]. Lin et al. demonstrated that Gd chelates loaded into MSNPs had better T_1 and T_2 relaxivity values compared to SSNPs with similar Gd agents and successfully used these nanoparticles for imaging the aorta and liver in mice [14]. Torresan et al. developed FeAu nanoparticles coated with thiolated PEG for use as CT/MRI contrast agents in mice, showing low particle accumulation in the liver and spleen while CT measurements outperformed iopromide [15]. Other alloy MNPs, such as FePt and FeNi, also exhibited high superparamagnetic properties with low toxicities as MRI contrast agents [16].

2.4 FMNs in Diagnostics

Early diagnosis is essential for effective treatment, as many critical conditions are detected too late, leading to preventable deaths. Accurate diagnostic assays are lacking, with MRI offering high resolution but low sensitivity and specificity, and PCR tests being highly sensitive and specific but time-consuming [17].

FMNs provide promising solutions for molecular diagnosis, enabling faster and simpler tests through magnetic separation, as shown in Fig. 2.2. They also enhance the sensitivity and specificity of MRI.

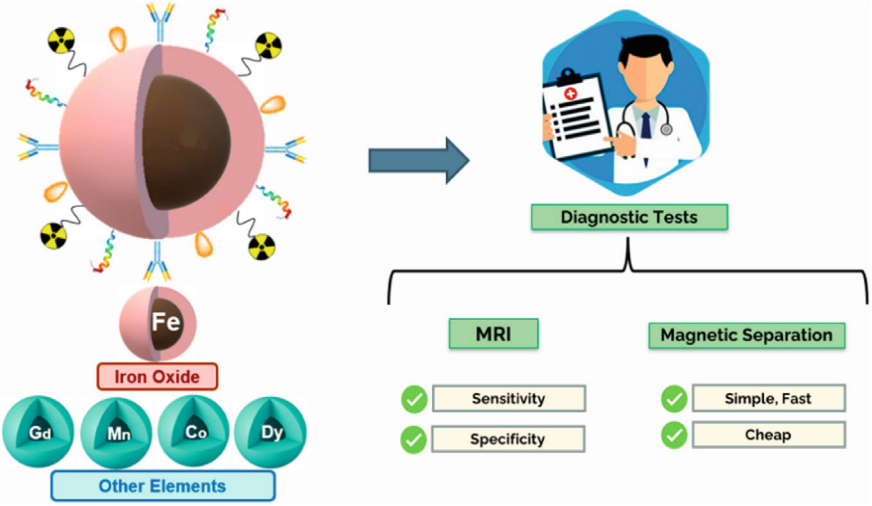

Fig. 2.2 Magnetic nanoparticles: a versatile tool for diagnostic tests in various imaging techniques Ref. [17] © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open-access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/). (All images are original and credited to the authors.)

Chen et al. developed a highly sensitive immunosensor that employs $CoFe_2O_4$ nanoparticles conjugated with an anti-CEA antibody [18]. These $CoFe_2O_4$ nanoparticles can be incorporated into biosensors to enhance sensitivity and specificity, speeding up the process and lowering the detection limit. Furthermore, $CoFe_2O_4$ nanoparticles can detect specific DNA strands, identifying point mutations and single-nucleotide polymorphisms without the need for time-consuming PCR methods. In addition, He et al. developed an immunosensor for detecting N-terminal pro-brain natriuretic peptide (NT-proBNP), a vital diagnostic and prognostic marker for heart failure. This immunosensor showcased a wide detection range, high sensitivity, and good reproducibility [19].

Long and colleagues have investigated methods to effectively isolate and enrich phosphopeptides from complex samples. FMNs have been examined as tools to enhance phosphopeptide signals and minimize impurity interferences, crucial for early disease diagnosis. Studies showed $CuFeMnO_4$ nanoparticles were effective in neutral and acidic conditions, and Mn-doped Fe_2O_4 microspheres also exhibited good reusability and selectivity for phosphopeptides [20]. Bai et al. developed amino-functionalized MNPs for DNA separation, achieving 4–5 times higher DNA adsorption efficiency compared to silica-coated iron oxide nanoparticles (IONPs). SiO_2 nanoparticles coated with IONPs and silica showed improved accumulation and separation yield under a magnetic field, enhancing stability and water solubility [21].

2.5 Functionalized Magnetic Nanomaterials (FMNs)—Tissue Engineering and Regenerative Medicine

Nanotechnology in tissue engineering integrates nanoparticles into nanofibers, creating functional organoids for molecular screening and regenerative applications. Magnetic nanoparticles enhance tissue regeneration through guided bioactive molecule delivery. Challenges include replicating in vivo tissue characteristics and current 2D culture limitations. A universal 3D cell culture technique using magnetic particles shows promise. Koudan et al. showed that cells with non-toxic nanomaterials can create viable 3D tissue spheroids. These spheroids maintain fluorescent microcapsules with magnetic nanoparticles without cytotoxic effects. The dense nanoparticles in the microcapsules preserve the spheroids' magnetic properties. Magnetic spheroids can be utilized for magnetic patterning and tissue-engineering biofabrication (Fig. 2.3) [22].

Magnetic particles hold promise for assembling complex tissues without the need for chemical cell alteration or cell-specific materials. However, several challenges need to be addressed: (i) *Biocompatibility*: Issues with metallic cores can be mitigated using polymeric coatings, hydroxyapatite shells, and choosing biocompatible cores like Fe_2O_3 or Fe_3O_4. (ii) *Immunological Reactions*: Surface charge alterations, functionalization, and neutralization with PEG or acetylation can help mitigate immune responses. (iii) *Accumulation and Biodegradability*: Strategies like functional group coatings or lipids can improve macrophagic uptake and renal clearance to address inefficient biodegradation and clearance, which can otherwise cause organ toxicity [23]. Despite these strategies, significant challenges remain for effectively using magnetic nanoparticles in tissue regeneration therapies.

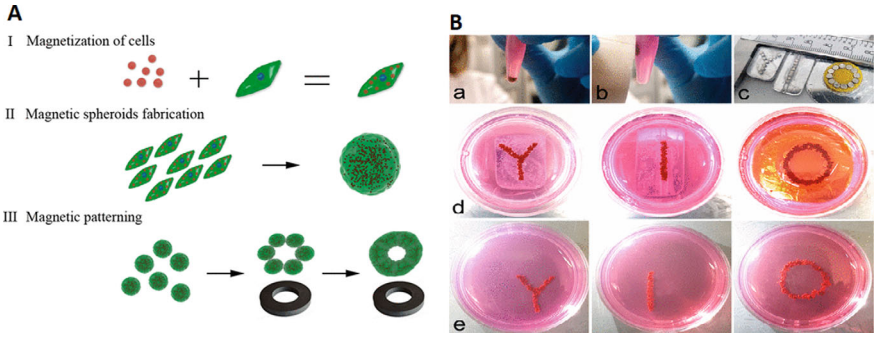

Fig. 2.3 Magnetic nanoparticle-based spheroid patterning involves the following steps: **A** The technique used to create magnetic spheroids. **B** Arrangement of tissue spheroids that are labeled with 12 magnetic microcapsules per cell under the influence of an applied magnetic field. (All images are original and belong to the authors.) Reprinted with permission from Ref. [22], 2021 Copyright © 2021, American Chemical Society

2.5.1 FMNs as Tissue Engineering Scaffolds

Tissue engineering aims to restore functional tissue at damaged sites using seed cells, growth factors, and 3D biodegradable scaffolds. While this method is essential for tissue regeneration and healing, a significant challenge is that cells often remain on the scaffold's surface and do not penetrate it. Recent research, however, has shown that a magneto-mechanical drive can direct cells to the scaffold's center, potentially overcoming this limitation. Parfenov et al. developed a technique using magnetic force to seed cells onto a porcine acellular carotid artery stent. The stent was submerged in a suspension of magnetically labeled cells, leading to increased cell adhesion due to iron oxide nanoparticle absorption. Additionally, chitosan-coated iron oxide nanoparticles enhanced the penetration of human osteoblasts into 3D scaffolds, improving cell interaction and accelerating the cell proliferation cycle. This magnetic approach shows significant potential for advancing bone tissue repair and regeneration, providing a valuable theoretical foundation for further research and clinical applications [24].

Fernandes et al. created magnetic nanocomposite scaffolds made of iron oxide nanoparticles and polycaprolactone. These scaffolds showed improved cell adhesion, increased alkaline phosphatase activity, and higher expression of osteogenesis-related genes compared to pure polycaprolactone scaffolds [25]. Gao et al. explored the nano-deformation of IO-OA/PLGA nanocomposites under static magnetic fields, discovering that magnetic mechanical stimulation significantly enhanced the osteogenic differentiation of MC3T3-E1 cells [26]. Cojocaru et al. investigated the combined effects of calcium phosphate composites with magnetic nanoparticle inclusions for bone tissue engineering [27]. Bigham et al. utilized a Mg_2SiO_4-$CoFe_2O_4$ nanocomposite scaffold as a multifunctional magnetic scaffold to eliminate residual bone cancerous tissues post-surgery [28].

2.5.2 Advancements in Stem Cell Therapy with FMNs

Recently, stem cell therapy has been proposed for repairing large bone defects. While successful in animal models, traditional stem cell transplantations have not shown comparable clinical results. Effective treatment requires maintaining stem cells' long-term characteristics, ensuring stable cell phenotypes, and reducing cell death at defect sites post-transplantation.

2.5.2.1 Materials Science and Chemical Biology Advances

Researchers are investigating the use of iron oxide nanoparticles with external magnetic fields to control and study stem cells. These nanoparticles affect cell adhesion, proliferation, movement, and osteogenic differentiation and are useful for

in vivo tracking and monitoring. Liu et al. demonstrated that Fe_3O_4/BSA particles enhance osteogenesis under magnetic fields, which is promising for stem cell-based bone regeneration therapies [29].

2.5.2.2 Cardiac Tissue Regeneration

Nanotechnology is advancing cardiovascular regeneration, focusing on alternative therapies for blood vessels, heart valves, and myocardium. Nanoparticle probes enable noninvasive imaging of cardiovascular targets, aiding diagnosis and treatment monitoring [30].

2.5.2.3 Bone Regeneration

Stem cell therapy for bone defects is effective in animal models but faces clinical challenges. Iron oxide nanoparticles improve stem cell characteristics and support adhesion, proliferation, and differentiation. They also aid in the precise delivery of labeled cells or medications and visualization via MRI [3].

2.5.2.4 Nervous System Regeneration

Stem cells, progenitor cells, and differentiated cells treat neurodegenerative diseases and brain injuries. Iron oxide nanoparticles enhance brain tissue therapy and drug delivery, with labeling techniques enabling tracking and monitoring through imaging methods like MRI, PET, and multiphoton microscopy [3].

2.6 Functionalized Magnetic Nanomaterials (FMNs)—Magnetic Hyperthermia

Magnetic nanoparticles (MNPs), including SPIONs, are important in biomedicine due to their low toxicity and good biocompatibility. They are used for cell separation, MRI contrast, targeted drug delivery, and localized magnetic hyperthermia (HT) for cancer treatment. HT heats MNPs to induce apoptosis in tumor tissues, enhancing immune responses and improving tumor blood flow, though thermal ablation at higher temperatures is less suitable. While precise control methods are still needed, biodegradable NPs are being developed for more effective HT, safely delivering thermo-therapeutic substances within tumors [31].

2.6.1 Magnetic Hyperthermia for Cancer Treatment

FMNs are being explored for hyperthermia treatment, using an external magnetic field to generate localized heat that targets cancer cells while sparing healthy tissues. Hyperthermia (HT) selectively targets tumor cells, enhancing their sensitivity to radiation therapy (RT) and chemotherapy (CT), with minimal impact on normal tissues. Cancer accounted for nearly 10 million deaths worldwide in 2020 [32]. Current treatments include surgery, CT, and RT, but are limited by toxicity, drug resistance, and low efficacy. HT has gained interest as a non-invasive cancer therapy, with early clinical studies dating back to 1891 by William Coley using "Coley's toxin". Hyperthermia (HT) has been used in clinical cancer treatment, though maintaining precise local temperature control is difficult. HT is categorized into three types: whole-body, regional, and local. Whole-body HT employs heating blankets and thermal chambers, often as an additional treatment for metastatic diseases. Regional HT involves using heated fluids and anticancer drugs to perfuse the peritoneal cavity. However, both whole-body and regional HT have limitations in clinical use due to severe side effects like gastrointestinal symptoms and cardiac complications. Hyperthermia (HT) induces cellular changes that disrupt homeostasis and lead to cell death, with the extent of damage dependent on temperature. Moderate temperatures (39–42 °C) are generally non-lethal, while temperatures above 42 °C can kill cells. HT causes cell damage by unfolding proteins, leading to aggregation and affecting crucial processes such as DNA synthesis, repair, transcription, RNA processing, and translation, ultimately causing cell cycle arrest and death. Additionally, HT disrupts the cytoskeleton, alters membrane permeability, and induces metabolic changes, resulting in decreased energy production and increased levels of intracellular sodium (Na^+), hydrogen (H^+), and calcium (Ca^{2+}) [33].

2.6.2 The Application of Functionalized Magnetic Nanomaterials (FMNs) for Locally Induced Hyperthermia (HT)

Magnetic hyperthermia (MHT) utilizes FMNs and an alternating magnetic field (AMF) to produce localized heat, effectively targeting cancer cells while preserving healthy tissues. MNPs can be functionalized to target tumor cells specifically, and their properties can be adjusted for improved outcomes. FMNs enhance hyperthermia (HT) effectiveness by creating temperature gradients in tumors, avoiding damage to healthy tissues due to their small size and high reactivity. They absorb heat from external sources, concentrating it on tumors in a process called inside-out HT. Examples include iron oxide, gold nanoparticles, and carbon nanotubes. FMNs use magnetic coupling to absorb and release heat, safely targeting cancer cells without significant energy deposition in healthy tissues [34] (Fig. 2.4).

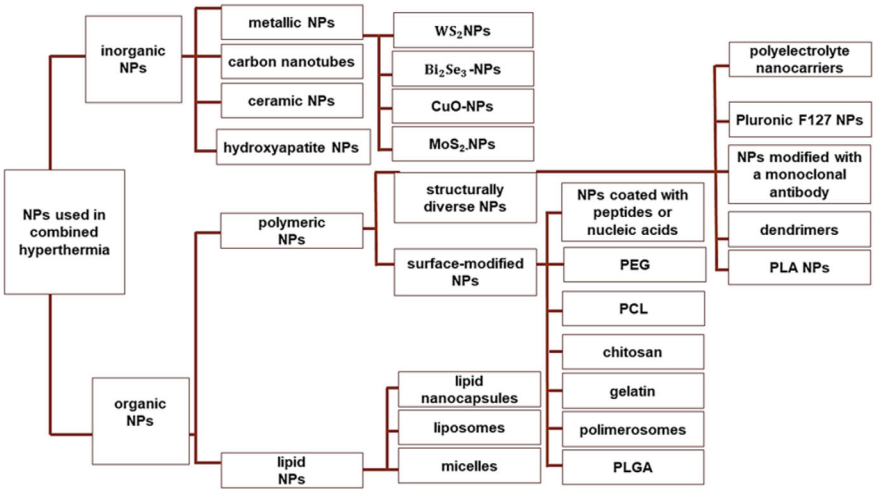

Fig. 2.4 Comprehensive classification of nanosystems for HT (all images are original and belong to the authors) Ref. [34] © 2024 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open-access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY-4.0) license (https://creativecommons.org/licenses/by/4.0/)

2.6.3 NP-Based MHT—Combination Therapies

One key clinical consideration in magnetic hyperthermia therapy (MHT) is the impact of increased temperature on blood flow within tumors and surrounding tissues. Combining MHT with treatments like chemotherapy (CT), radiotherapy (RT), photothermal therapy, or gene therapy enhances effectiveness. MHT combined with CT increases drug concentrations, inhibits DNA repair, and reduces apoptosis-resistant cancer cells. FMNs with MHT improve blood flow, accelerating drug delivery and release in cancer tissues. Combining MHT with RT has proven effective in treating prostate cancer, enhancing treatment efficacy and survival rates. Polymeric FMNs target genetic material delivery, restoring cellular functions and inducing programmed cell death. Increasing internal temperature through photothermal therapy shows synergistic effects when combined with FMNs and laser irradiation [35].

2.7 Functionalized Magnetic Nanomaterials (FMNs)—Biosensing and Detection

Biosensors detect and measure molecules and microorganisms by converting biological interactions into electrical signals using bioreceptors. Electrochemical and optical transductions offer high sensitivity and miniaturization but face challenges

in maintaining sensitivity and selectivity over time. FMNs and beads address these issues, enhancing specificity and sensitivity. FMNs combined with electrochemical read-out methods, like ELIME (enzyme-linked immuno-magnetic electrochemical), improve analyte isolation, concentration, and detection. MNPs are also significant in microfluidic systems, enhancing analytical performance and cell separation efficiency [36].

Peng et al. developed a chitosan-functionalized nanocomposite for glucose determination, featuring magnetic nanoparticles, chitosan, β-cyclodextrin (Fe3O4-CS-CD), and multi-walled carbon nanotubes. This sensor showed excellent biocompatibility, nontoxicity, high mechanical strength, low detection limit, broad linear range, high sensitivity, excellent selectivity, and long-term stability [37]. Di Tocco et al. developed a functionalized electrochemical biosensor for triglyceride (TG) detection, using lipase immobilized on chitosan-coated magnetic nanoparticles (MNPs) dispersed in a matrix of multiwalled carbon nanotubes/pectin (MWCNT/Pe) modified with copper oxide on a glassy carbon electrode (GCE). The sensor demonstrated good sensitivity for determining TGs in human serum samples [38]. Wang et al. developed a PEG-mediated APBA-functionalized magnetic nanomaterial (APBA-PEG-MN) for detecting Staphylococcus aureus using magnetic separation and fluorescence analysis, with a limit of detection (LOD) of 270 CFU/mL in various matrices [39].

Polypyrrole (Ppy) and chitosan-coated Fe_3O_4 were used to create a platform for immobilizing glucose-6-phosphate dehydrogenase on pencil graphite electrodes. The resulting biosensor showed good linear response, high selectivity, and recovery for glucose-6-phosphate (G6P) detection [40]. Polyaniline PANI/magnetic graphene (MG) composites were synthesized to immobilize laccase for detecting phenols in various samples, exhibiting high sensitivity and a detection limit of 2.94 μM [41].

Sardaremelli et al. developed an electrocatalytic reduction and enzymatic biosensing strategy for hydrogen peroxide (H_2O_2) using polydopamine-modified magnetic nanoparticles (PDA-MNPs) and a poly(l-arginine/toluidine blue) film-modified glassy carbon electrode, achieving a detection range of 0.5–30 μM and a low limit of quantification at 0.23 μM in human plasma samples [42]. 3D hierarchically porous magnetic molybdenum trioxide–pDA-gold functionalized nanospheres (3D mag-MoO3–pDA@Au) were used in a Raman scattering sensing platform for ultrasensitive detection of SARS-CoV-2 [43]. A biosensor with gold nanoparticle-loaded magnetic reduced graphene oxide (MrGO@AuNPs) was developed for detecting bisphenol A (BPA) with high sensitivity and a detection limit as low as 0.141 pg/mL [44]. Quantum dots (QDs) integrated into magnetic nanomaterials were also used in a prototype biosensor for detecting *E. coli* in water samples, showing potential for food sample applications [45]. The main benefits of magnetic nanomaterials are their enhanced sensitivity and detection speed, affordability, and user-friendliness, even for those with minimal training. Moreover, magnetic nanoparticles boast an almost endless shelf-life, unlike biosensing methods that rely on fluorescent or radioactive materials, and they are easier to assemble and integrate with microfluidics. Magnetic nanoparticles are transforming biosensor technology, enhancing sensitivity, speed,

and cost-effectiveness. They are used in medical diagnostics and bioterrorism detection. Advances include biologically relevant coatings for targeted drug delivery and magneto-optic biosensors that detect chemical binding events in real time.

2.8 Functionalized Magnetic Nanomaterials (FMNs)—Toxicology

Toxicology studies determine the harmful effects of agents on animals, humans, and the environment. Cellular toxicity manifests as altered morphology, reduced mitochondrial activity, and membrane leakage, which negatively impact cell survival and therapies [46]. In treatments, FMNs raise concerns about their potential migration, entry, and accumulation within organs, which may trigger inflammatory or immune responses. Absorbed FMNs can cause cytotoxic reactions, and their physical characteristics, such as shape and size, can lead to hazardous reactions. FMNs pose risks due to oxidative stress resulting from an imbalance of antioxidants and oxidants [47]. Oxidative stress, the main cause of reactive oxygen species (ROS) production, damages cellular proteins, lipids, and nucleic acids, leading to disease and cell death [48]. ROS sources include the MNP surface, metal ion loss, and oxidant release during enzymatic breakdown [49]. Isolated iron oxide MNPs can promote ROS production, affecting cell metabolism and enhancing apoptosis, but ROS can also be used in cancer treatment [50].

2.9 Concluding Remarks and Future Perspectives

FMNs have shown significant potential in biomedical applications such as drug delivery, imaging, tissue engineering, and cancer treatment. Their magnetic properties enable targeted therapies, improved diagnostic accuracy, and minimally invasive procedures. FMNs have advanced hyperthermic treatments and biosensing, addressing contemporary healthcare challenges. However, concerns about biocompatibility, stability, and potential cytotoxicity need further investigation.

Future research should optimize FMNs' functionalization techniques to enhance specificity and efficiency in biomedical applications. Developing biodegradable, non-toxic magnetic nanomaterials is crucial for reducing side effects and improving patient safety. Integrating FMNs with technologies like artificial intelligence, personalized medicine, and nanorobotics could revolutionize clinical applications. Rigorous preclinical and clinical trials are necessary to validate efficacy and secure regulatory approval. Addressing these challenges will enable FMNs to transform modern healthcare, enhancing patient outcomes and therapeutic precision.

Abbreviations

AMF	Alternating Magnetic Field
AMLs	Antibody-Conjugated Magnetoliposomes
APBA	*m*-Aminophenylboronic Acid
BSA	Bovine Serum Albumin
CKD	Chronic Kidney Disease
CNS	Central Nervous System
CT	Chemotherapy
DTPA	Diethylenetriamine Pentaacetic Acid
ECM	Extracellular Matrix
ELIME	Enzyme-Linked Immuno-Magnetic Electrochemical method
FMNs	Functionalized Magnetic Nanomaterials
HT	Hyperthermia
IARC	International Agency for Research on Cancer
IDA	Iron Deficiency Anemia
IONPs	Iron Oxide Nanoparticles
IO-OA/PLGA	Iron Oxide-Oleic Acid/Poly(lactic-co-glycolic acid)
MCs	Magnetic Clusters
MHT	Magnetic Hyperthermia Therapy
MNPs	Magnetic Nanoparticles
MRA	MR Angiography
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MWCNT/Pe	Multiwalled Carbon Nanotubes/Pectin
NPs	Nanoparticles
PEG	Polyethylene Glycol
PNS	Peripheral Nervous System
RT	Radiotherapy
SLN	Sentinel Lymph Node
SPIONs	Superparamagnetic Iron Oxide Nanoparticles
SSNPs	Solid Silica Nanoparticles

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