MINI-REVIEW

Magnetic iron oxide nanomaterials: A key player in cancer nanomedicine

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Funding information
Jiangsu Province Policy Guidance Plan, Grant/Award Number: BZ2019014; Six Talent Peak Innovation Team in Jiangsu Province, Grant/Award Number: TD-SWYY-009; Strategic Research Fund of City University of Hong Kong, Grant/Award Number: CityU_700514; Research Impact Fund of Hong Kong Research Council, Grant/Award Number: R1020-18F; Guangdong Provincial Science and Technology Project, Grant/Award Number: 2017B020226001; Basic Research Project of Shenzhen Knowledge Innovation Program, Grant/Award Number: JCYJ20170818095453642

Abstract
Magnetic iron oxide nanomaterials are among the most widely studied candidates for cancer nanomedicine, because of not only their great biocompatibility and abundance of raw materials, but also their diverse physicochemical properties and biological effects. Represented by magnetite and maghemite, various iron oxide-based magnetic nanomaterials have been developed for cancer diagnosis and treatment. This mini review presents an up-to-date overview of magnetic iron oxide-based cancer nanomedicines with an emphasis on bioimaging and therapy.

KEYWORDS
Cancer nanomedicine, iron oxide nanomaterials, magnetic particle imaging, magnetic resonance imaging, magnetic targeting, thermal therapy
Cancer is a worldwide public health problem and is the leading cause of death in most countries. During the past decades, great efforts have been made in engineering nanomaterials to diagnose and treat cancers. Among the various nanoplastorms, magnetic iron oxide nanoparticles (MIONs, typically refer to magnetite- or maghemite-based nanomaterials) have attracted broad interest due to their favorable biocompatibility, abundance of raw materials, and especially, their unique physicalchemical properties and biological effects. MIONs can respond to static or dynamic magnetic fields, which gives rise to diverse functionalities, such as magnetic field-guided targeting, $T_1/T_2$-weighted magnetic resonance imaging (MRI), magnetic particle imaging (MPI), and magnetothermal therapy. Besides, iron oxide nanomaterials can be applied for photothermal imaging and therapy due to their intrinsic optical properties. Benefiting from the chemical activities of iron oxides, smart nanomaterials in response to endogenous stimuli (eg, pH, $H_2O_2$, and glutathione) could be designed for tumor-specific theranostics, thus maximizing the therapeutic efficacy and minimizing side effects. Moreover, recent studies have revealed the biological significance of nanomaterials, where MIONs-triggered immunological response and MIONs-regulated cell death provide novel approaches in cancer management.

This mini review discusses the recent research progress in MIONs-based cancer nanomedicines based on the magnetic properties, starting with an overview of the diversity and surface engineering of MIONs, following with their applications in cancer diagnosis and treatment, focusing on MRI, MPI, magnetothermal therapy, and magnetic field-guided targeting therapy.
hybrid membrane has been reported for MIONs surface modification. Benefiting from the inherent functional groups on biomembranes, the hybrid nanoparticles integrated capabilities of both immune evasion (originated from platelet membrane) and active cancer targeting (originated from cancer stem cells). The nanoplatform showed excellent antitumor activity in head and neck squamous cell carcinoma-xenograft animal model.

3 MIONs FOR CANCER DIAGNOSIS AND THERAPY

3.1 Cancer diagnosis

MIONs have been extensively applied to cancer diagnostic purposes for imaging of primary to metastatic tumor, as well as cancer-related immune cells. Owing to the
property diversity, MIONs have been proved to be powerful probes in many bioimaging applications, represented by MRI and MPI. Additionally, multimodal imaging can be realized by integrating MIONs with other functional materials or radioactive ions.\textsuperscript{53,54} Below, we discuss recent progress in MIONs-based cancer diagnostic nanoplatforms with a focus on MRI and MPI.

3.1.1 Magnetic resonance imaging

MRI is a well-established technique capable of quantitative and multidimensional imaging of lesions located in deep tissue. Its sensitivity and accuracy have been remarkably improved by the development of various contrast agents.\textsuperscript{55} MIONs have been widely investigated as MRI contrast agents since the 1980s with several forms of MIONs-based nanoagents having been approved for clinical MRI application. During MRI, the endogenous hydrogen atoms are first excited by a radio frequency pulse and then allowed to return to equilibrium state via two relaxation processes: longitudinal $T_1$ (spin-lattice) and transverse $T_2$ (spin-spin) relaxations. MIONs provide the $T_1$ and $T_2$ contrast by generation of local magnetic field and shortening the relaxation time, which is expressed by $r_1$ or $r_2$ relaxivity. MRI contrast agents can be classified according to their action mechanisms: (a) positive contrast agents, which mainly accelerate the $T_1$ relaxation and generate bright images, and (b) negative contrast agents, which mainly accelerate the $T_2$ relaxation and generate dark images. Due to the gigantic magnetic moment, most available iron oxide nanomaterials are $T_2$ contrast agents. Several methods have been demonstrated effectively in enhancing the performance of $T_2$ contrast agents in cancer diagnosis: (a) increasing the saturation magnetization of MIONs by improving their crystallinity or ion-doping, (b) surface modification to increase nanoparticle dispersibility and accessibility of surrounding water molecules, and (c) immobilizing targeting ligands to increase tumor accumulation.\textsuperscript{5,6} However, current clinical application of $T_2$ MRI is still hampered by the fact that the generated dark signal can be confused with endogenous factors (eg, air, calcification, and hemorrhage). On the other hand, $T_1$ MRI is preferred for accurate high-resolution imaging in clinics. Ultrasmall magnetite nanoparticles with diameters less than 5 nm are candidates for $T_1$ MRI due to their low magnetization induced by the strong surface spin-canting effect. Doping Mn or Gd ions into the ultrasmall Fe$_3$O$_4$ has been proved to be effective in improving $T_1$ MRI contrast by generating a fully spin-canted structure.\textsuperscript{56,57} In addition, assembling USIONs into nanoparticles with a diameter of 100 nm could effectively increase their tumor accumulation, thus enhancing the $T_1$ MRI contrast.\textsuperscript{58} Despite the improvement in MRI techniques and contrast agents, a single imaging modality is unable to provide comprehensive information of lesions. Simultaneous acquisitions of both $T_1$ and $T_2$ signals have been pursued to obtain complementary information from tumor tissues. Recently, Lu and colleagues reported an iron oxide nanocluster that was assembled with the assist of pH-responsive i-motif DNA (termed as RIAs).\textsuperscript{59} Upon exposure to the acidic tumor microenvironment, the nanoclusters are disassembled, which lead to a significant decrease in relaxivity ratio ($r_2/r_1$), thus switching from $T_2$ to $T_1$ contrast (Figure 2A). This smart nanoplatform has been applied to detecting early stage small hepatocellular carcinomas (HCC) in a xenograft animal model (Figure 2B). One problem for iron oxide-based MRI is the overlapping signal from endogenous iron. Masthoff et al combined MRI with ex vivo laser ablation inductively coupled plasma-mass spectrometry imaging by using nonradioactive $^{57}$Fe-labeled MIONs as the detection probes. This method could differentiate the administered iron oxides from endogenous iron ($^{56}$Fe) unambiguously.\textsuperscript{60}

To improve the detection specificity, other imaging modalities have been integrated with MRI for cancer diagnosis.\textsuperscript{33,61} For example, indocyanine green-loaded Fe$_3$O$_4$ nanoparticles enabled optical imaging and photothermal imaging.\textsuperscript{9} Radiolabeling of iron oxides could be used for radionuclide imaging, including positron emission tomography and single-photon emission computed tomography.\textsuperscript{62} Nanocomposites integrating MIONs with gold have been investigated for computed tomography and photoacoustic imaging.\textsuperscript{63}

3.1.2 Magnetic particle imaging

MPI is the first completely new imaging modality in nanomedicine that was invented by Gleich et al.\textsuperscript{64} Different from MRI, MPI detects the location and concentrations of SPIONs directly with time-varying magnetic fields, thus the role of SPIONs in MPI is as “tracer agents” rather than “contrast agents.” The principle of MPI is that SPIONs can be magnetized by external magnetic field instantaneously and induce a nonlinear response in near-zero magnetic field. Compared with existing imaging modalities, MPI is promising for cancer diagnosis because it integrates several advantages such as zero background signal, zero signal attenuation with increasing tissue depth, linear quantitativity, high sensitivity, and no ionizing radiation.\textsuperscript{54} Yu et al first demonstrated the application of MPI for in vivo tumor imaging with systemically administrated SPIONs.\textsuperscript{65} Recent advances in MPI are highly dependent on the relaxation behavior and pharmacokinetics of tracers. Therefore, great efforts have been devoted to optimizing SPIONs and their surface modification. Song et al
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**FIGURE 2** MIONs for cancer diagnosis and therapy. (A) Relaxivity of RIAs in solutions with different pH values. (B) In vivo diagnosis of small HCC with RIAs-based T<sub>1</sub> MRI. Reproduced with permission. Copyright 2018, American Chemical Society. (C) Comparison of MPI signal of nerve density in prostate cancer 24 h postsystemic injection of SPIONs with PSN and without PS active targeting ligand. Reproduced with permission. Copyright 2020, American Association for the Advancement of Science. (D) Workflow of SPIONs-based theranostic platform for MPI-guided magnetothermal therapy. Reproduced with permission. Copyright 2018, American Chemical Society. (E) Comparison of heating efficiency of magnetic hyperthermia (MHT), optical excitation (LASER), and magnetophotothermal treatment (DUAL) in cancer cell suspensions (up) and tumor bearing mice (down). Reproduced with permission. Copyright 2016, American Chemical Society. (F) Illustration of the action mechanism of FVIO-mediated mild magnetic hyperthermia-sensitized immune checkpoint therapy. Reproduced with permission. Copyright 2019, American Chemical Society

Systematically investigated the influence of reaction conditions of SPIONs on their MPI performance. It was found that the cubic Fe<sub>3</sub>O<sub>4</sub> structure with high crystallinity is required for high MPI signals, and their tailored nanoparticles showed much higher MPI intensity than commercial MPI tracer (Ferucarbotran) and MRI contrast agent (Feraheme). The MPI signal could be further enhanced by immobilizing targeting ligands onto SPIONs. For example, nerve-binding peptide (NP41)-decorated SPIONs have been used for the detection of nerve density in prostate cancer, which showed much stronger MPI signal than the bare SPIONs (Figure 2C). Notably, magnetothermal therapy could be integrated with MPI to construct a SPIONs-based theranostic platform. The pioneer work was demonstrated by Tay et al. First, the treatment plan was laid out with the guidance of quantitative MPI imaging. Subsequently, MPI
gradients were utilized for spatial localization of magnetic hyperthermia to selected regions for accurate treatment (Figure 2D). This theranostic platform addressed the key challenge in conventional magnetothermal therapy, that is, difficulty in localizing hyperthermia to target lesions without collateral damage to healthy tissues, especially the clearance organs.

3.2 | Cancer therapy

Owing to their property diversity, MIONs provide several modalities to combat cancers effectively, including magnetothermal therapy, photothermal therapy, chemodynamic therapy, immunotherapy, and so forth. In addition, MIONs can be guided by external magnetic field to target tumor tissues. According to the various reported cancer therapies, MIONs work either independently or as an adjuvant in conjunction with other anticancer modalities. In this subsection, we focus on the magnetic property-related anticancer therapies of MIONs, and mainly discuss recent progress of their contributions in magnetothermal therapy and magnetic field-guided targeting therapy.

3.2.1 | Magnetothermal therapy

The use of heat as an anticancer treatment became popular in the 19th century and is undergoing an unprecedented revolution with the development of nanotechnology. Among the various heating modalities, MIONs-mediated magnetothermal treatments have attracted broad interests due to their unlimited tissue penetration and ability to be controlled and monitored remotely. Under an alternating magnetic field, MIONs mediate the conversion of electromagnetic energy to heat via Néelian and Brownian relaxations. One of the aims in developing magnetothermal therapies is to enhance the heating efficiency of MIONs in order to reach desirable temperature with minimum dosage and power density. Recent progress in optimizing MIONs, such as synthesizing anisotropic MIONs, nanoassembly, core-shell nanostructures, and ion-doped MIONs, has achieved unprecedented magnetic heating efficiency (≥1 kW/g). However, the dynamical magnetic response of MIONs is confined by the complex biological environments. For example, the Brownian relaxation of MIONs is inhibited by endosomal confinement effect. One solution is to combine both magnetothermal and photothermal effects of MIONs, that is, the magnetophotothermal approach, to enhance the overall heating efficiency. This concept was first presented by Espinosa et al. In vitro experiment showed that the additional 808-nm laser irradiation (power density: 0.8 W/cm²) leads to a 15-fold amplification of heating efficiency as compared with magnetic hyperthermia alone. This remarkable heating effect was further observed in nanoparticle-internalized cancer cells and tumor-bearing mice model (Figure 2E).

Interestingly, magnetic hyperthermia-mediated tumor ablation also elicits systemic antitumor immunity. Liu and colleagues developed a ferromagnetic vortex-domain iron oxide nanoring (FVIO)-based therapeutic platform, in which a mild magnetic hyperthermia (43–44 °C) generated from FVIO could induce cancer cell apoptosis and expose calreticulin to cell surface, releasing an “eat-me” signal to elicit phagocytosis, thus inducing immunogenic cell death. Moreover, the therapeutic effect could be further improved by cooperation with programmed death ligand 1 checkpoint blockade (Figure 2F). In vivo experiments on 4T1 xenograft mice demonstrated the superior therapeutic effectiveness of this method, which not only eradicated the primary tumors, but also inhibited the growth of distant tumors and lung metastasis.

3.2.2 | Magnetic field-guided targeting therapy

One of the major concerns in cancer nanomedicine is the tumor targeting efficiency, which influences both therapeutic efficacy and biosafety in clinical applications. Tremendous efforts have been devoted to enhance tumor targeting efficiencies. Among the various approaches, magnetic targeting is considered a promising approach that can be conducted in a spatiotemporal controllable manner. Taking advantage of their magnetic responsiveness, MIONs can be manipulated and guided to the target tissue with external magnetic field. Due to the inherent transparency of biological tissues to magnetic field, magnetic targeting can be performed remotely and noninvasively. Compared to other tumor targeting modalities using the biochemical differences between tumor and normal tissues (eg, pH value, H₂O₂ level, O₂ concentration, and biomarkers), magnetic targeting is more flexible and free from limitation of specific receptor expression and tumor heterogeneity. Besides, the tumor accumulation of magnetic nanoparticles can be monitored in real time by MRI. One problem in molecular recognition-based active targeting is that the excessive ligand immobilization may impair the tumor targeting capability of nanoparticles. Therefore, to further enhance targeting efficiency of nanoagents, integrating multiple targeting modalities could be a practical solution. For instance, c(RGDyK)- and D-glucosamine co-immobilized nanoprobe (Fe₃O₄@RGD@GLU) has been developed for multi-targeted magnetothermal therapy, wherein
| Name                          | Formulation                                      | Clinical trials ID | Applications                                                                                      | Disease                        | Phase       | Start/Completion date |
|-------------------------------|--------------------------------------------------|--------------------|--------------------------------------------------------------------------------------------------|---------------------------------|-------------|-----------------------|
| Ferucarbotran (Resovist, Clavist) | SPIONs coated with carboxydextran                  | NCT00307866        | Enhanced MRI for detection of primary or secondary hepatic malignancies.                        | Hepatic Neoplasm                | Phase 3     | 2001/2003             |
| Ferumoxide (Feridex I.V., Endorem) | SPIONs (non-stoichiometric magnetite) coated with dextran | NCT00243594        | Use magnetically labeled DCs and MRI to monitor DC vaccines-based immunotherapy                 | Melanoma (Stage III or IV)      | Phase 1, Phase 2 | 1999/2009             |
| Ferumoxtran-10 (Combidx, Sinerem, Ferrotran) | USPIOs stabilized with dextran and sodium citrate | NCT00659334        | MRI for imaging brain tumors and the adjacent inflammatory lesions before neurosurgery.         | Brain Neoplasms                 | Phase 2     | 2000/2010             |
|                               |                                                  | NCT00188695        | MRI for detection of pelvic lymph nodes                                                          | Bladder neoplasms cervix neoplasms Prostatic neoplasms | Phase 1, Phase 2 | 2004/2006             |
|                               |                                                  | NCT00147238        | MRI for detection of pelvic lymph node metastases                                                 | Bladder Cancer Genitourinary Cancer Prostate Cancer | n.a.        | 2005/2007             |
|                               |                                                  | NCT004311047       | Enhanced MRI for detection of lymph node metastases of solid tumors                              | Pancreatic cancer Periampullary cancer | n.a.        | 2017/2021             |
|                               |                                                  | NCT004261777       | Enhanced MRI for detection of pelvic lymph node metastases in newly-diagnosed patients          | Prostate cancer                  | Phase 3     | 2020/2020             |

(Continues)
| Name                        | Formulation                                                                 | Clinical trials ID | Applications                                                                 | Disease                                                                 | Phase    | Start/Completion date |
|-----------------------------|------------------------------------------------------------------------------|--------------------|------------------------------------------------------------------------------|-------------------------------------------------------------------------|----------|-----------------------|
| Ferumoxytol (Feraheme, Rienso) | SPIONs coated with polyglucose sorbitol carboxymethylether                    | NCT00920023        | MRI to identify small and otherwise undetectable lymph node metastases       | Pancreatic cancer                                                      | Phase 4  | 2008/2013             |
|                             |                                                                                | NCT00769093        | MRI for imaging microvascular change in the brain and tumor                  | Brain Neoplasms (Recurrent high grade glioma)                           | Phase 1  | 2008/2014             |
|                             |                                                                                | NCT00978562        | MRI to describe the vascular properties of pediatric brain tumors           | Childhood brain neoplasm, recurrent childhood brain neoplasm            | n.a.     | 2009/2018             |
|                             |                                                                                | NCT01927887        | Enhanced MRI to identify small metastases in lymph nodes that are not usually observed on standard MRI | Follicular thyroid cancer lymph node metastasis                          | n.a.     | 2012/2016             |
|                             |                                                                                | NCT01895829        | MRI to detect the spread of cancer                                           | Head and neck cancer                                                   | Early    | 2013/2022             |
|                             |                                                                                | NCT02253602        | Enhanced MRI by combination of diffusion weighted MRI and $T_2$ MRI        | Esophageal neoplasms                                                   | n.a.     | 2014/2018             |
|                             |                                                                                | NCT02452216        | Enhanced MRI for assessing the inflammatory response of brain tumors and other central nervous system conditions | Brain neoplasms and other central nervous system disorders              | Early    | 2015/2017             |
|                             |                                                                                | NCT02689401        | MRI to detect lymph node metastases                                          | Esophageal cancer                                                      | Phase 1  | 2016/2016             |
|                             |                                                                                | NCT03179449        | Enhanced MRI for detection of inflammation (macrophage) in tumors           | Childhood brain neoplasm                                               | Early    | 2017/2022             |
|                             |                                                                                | NCT03280277        | Enhanced MRI for detection of advanced rectal cancer with enlarged or suspicious lateral pelvic lymph nodes | Rectal cancer (Stage III, IIA-IIIC)                                    | Phase 2  | 2018/2020             |
|                             |                                                                                | NCT02857218        | MRI before neoadjuvant chemoradiation therapy and again before esophagectomy | Esophageal cancer (Stage IIB-IIIC)                                     | Early    | 2018/2021             |
|                             |                                                                                | NCT04369560        | MRI for determination of bladder cancer stage                               | Urinary bladder neoplasms                                              | Early    | 2020/2022             |

(Continues)
| Name      | Formulation                          | Clinical trials ID | Applications                                                                 | Disease            | Phase          | Start/Completion date |
|-----------|--------------------------------------|--------------------|------------------------------------------------------------------------------|--------------------|----------------|------------------------|
| Sienna+   | SPIONs coated with carboxyldextran   | NCT02249208        | Determine the false negative rate and detection rate of sentinel lymph nodes with Sienna+ (tracer)/Sentimag (magnetic sensing probe) | Breast cancer      | Phase 3        | 2014/2016              |
|           |                                      | NCT03449615        | Identify lymph nodes with Sienna+/Sentimag                                  | Cutaneous malignant melanoma | n.a.           | 2015/2018              |
|           |                                      | NCT02612870        | Mark lymph nodes with Sienna+/Sentimag before surgery                       | Breast neoplasms   | Phase 4        | 2016/2016              |
|           |                                      | NCT03243435        | Native breast MRI to detect long-term uptake of contrast agents              | Breast cancer      | n.a.           | 2016/2017              |
| Magtrace  | SPIONs coated with carboxyldextran   | NCT02739425        | Sentinel lymph node biopsy with Magtrace (tracer)/Sentimag (magnetic sensing probe) | Breast Cancer      | n.a.           | 2016/2018              |
|           |                                      | NCT03898687        | Sentinel lymph node biopsy with Magtrace/Sentimag                           | Melanoma           | n.a.           | 2019/2020              |
| n.a.      | USPIOs                               | NCT01749280        | MRI to predict the growth of aneurysm                                       | Abdominal aortic aneurysm | n.a.           | 2011/2022              |
| MTC-DOX   | Magnetic beads attached with doxorubicin | NCT00041808       | Magnetic-guided chemotherapy                                                 | Colorectal neoplasm | Phase 1,       | 2001/2003              |
|           |                                      |                    |                                                                              | Esophageal neoplasm | Phase 2        |                        |
|           |                                      |                    |                                                                              | Stomach neoplasm    |                |                        |
|           |                                      |                    |                                                                              | Pancreatic neoplasm |                |                        |
|           |                                      |                    |                                                                              | Breast neoplasm     |                |                        |
|           |                                      |                    |                                                                              | Melanoma            |                |                        |
|           |                                      |                    |                                                                              | Sarcoma             |                |                        |
|           |                                      |                    |                                                                              | Gastrointestinal neoplasm |            |                        |
|           |                                      |                    |                                                                              | Lung neoplasm       |                |                        |
|           |                                      |                    |                                                                              | Liver neoplasm      |                |                        |
|           |                                      |                    |                                                                              | Cholangiocarcinoma  |                |                        |
|           |                                      |                    |                                                                              | Metastasis neoplasm |                |                        |
|           |                                      | NCT00034333        | Evaluate safety, tolerance, and efficacy of the MTC-DOX dosing strategy     | Hepatocellular carcinoma | Phase 2,       | 2002/Terminated       |
|           |                                      |                    |                                                                              |                    | Phase 3        |                        |

(Continues)
| Name Formulation | ClinicaltrialsID | Applications | Disease | Phase | Start/Completion date |
|------------------|------------------|--------------|---------|-------|-----------------------|
| n.a.             | NCT02033447      | Inject magnetic nanoparticles in prostate pathology specimens use MRI and CT to detect the retention and distribution of nanoparticles | Prostate cancer | Early Phase 1 | 2013/2015 |
| n.a.             | NCT04316091      | Neoadjuvant chemotherapy + SPIONs/spinning magnetic field. Evaluate tolerability, safety, and efficacy of the treatment | Osteosarcoma | Phase 1 | 2020/2023 |

Abbreviations: DC, dendritic cell; SPIONs, superparamagnetic nanoparticles; n.a., not available.

D-glucosamine recognized glucose transporter on cancer cell membrane, and c(RGDyK) proteins assisted nanoprobes to enter cancer cells via \( \alpha_\text{v} \beta_3 \)-mediated endocytosis. With the combination of dual-active and magnetic targeting, this nanoplatform showed superior theranostic performance over the control groups with single targeting mode.\(^81\)

With increasing attention to public health and demands of pharmaceutical industry, various nanomedicines are stepping from bench to bedside.\(^82\) We summarize the clinical trials of MIONs-based cancer diagnosis and therapy to provide references for future development of MIONs.

4 | CONCLUSION AND OUTLOOK

This mini review discussed recent advances in MIONs-based cancer nanomedicine, with a focus on MIONs design considerations as well as their applications in cancer diagnosis (MRI and MPI) and treatment (magnetothermal therapy and magnetic field-guided targeting therapy). By controlling the structure and composition of MIONs, the physicochemical properties of MIONs can be engineered to improve theranostic performance. In particular, MPI provides a novel tool for imaging-guided, site-specific magnetothermal therapy. Additionally, the discovery of immunological effect of magnetic hyperthermia deepened our understanding on biological effect of thermal therapy.

Despite the flourishing research progress in MIONs-based cancer nanomedicine, the clinical translation remains slow, and there are still significant challenges to be addressed. First, simplified synthetic method and the homogeneous products of MIONs are rarely achieved concurrently. The preparation of multifunctional MIONs with desired performance always requires complex synthetic processes or harsh reaction conditions. Therefore, developing controllable, repeatable, and scalable synthetic methods will facilitate commercialization of MIONs-based nanomedicine. Second, considering the clinical demand on early detection of cancer, the spatial resolution of MIONs-based bioimaging needs to be further improved for small cancer cell clusters or even single cell tracking. Third, the morphologies and sizes of MIONs influence both their magnetic responsiveness and hydrodynamic performances in vivo. The parameters of MIONs should be carefully selected and optimized for a successful magnetic targeting. Finally, there are still many unknowns in cancer biology involving nanomedicines. Better understanding of tumor heterogeneity and nano-bio interactions is required for overcoming various biological barriers in nanomedicine-based cancer diagnosis and therapy. We expect that the continuous development of this multidisciplinary field will bring more MIONs-based
nanomedicines close to the clinic and contribute to the war against cancer.

**CONFLICT OF INTEREST**
The authors declare no conflict of interest.

**ACKNOWLEDGMENTS**
The work was supported by Jiangsu Province Policy Guidance Plan (BZZ2019014), Six Talent Peak Innovation Team in Jiangsu Province (TD-SWYY-009), Strategic Research Fund (CityU_7005114) of City University of Hong Kong, Research Impact Fund (R1020-18F) of Hong Kong Research Grant Council, Guangdong Provincial Science and Technology Project (2017B020226001), and the Basic Research Project of Shenzhen Knowledge Innovation Program (JCYJ20170818095453642).

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How to cite this article: Liang C, Zhang X, Cheng Z, Yang M, Huang W, Dong X. Magnetic iron oxide nanomaterials: A key player in cancer nanomedicine. VIEW. 2020;1:20200046. https://doi.org/10.1002/VIW.20200046