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Review Article

Applications of Nanoparticles for MRI Cancer Diagnosis and Therapy

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Recent technological advances in nanotechnology, molecular biology, and imaging technology allow the application of nanomaterials for early and specific cancer detection and therapy. As early detection is a prerequisite for successful treatment, this area of research has been rapidly growing. This paper provides an overview of recent advances in production, functionalization, toxicity reduction, and application of nanoparticles to cancer diagnosis, treatment, and treatment monitoring. This review focuses on superparamagnetic nanoparticles used as targeted contrast agents in MRI, but it also describes nanoparticles applied as contrasts in CT and PET. A very recent development of core/shell nanoparticles that promises to provide positive contrast in MRI of cancer is provided. The authors concluded that despite unenviable obstacles, the progress in the area will lead to rapidly approaching applications of nanotechnology to medicine enabling patient-specific diagnosis and treatment.

1. Introduction

Despite many efforts, cancer is among the top three causes of death in modern society [1], demanding improved treatment, that currently includes surgery, chemotherapy, and various types of radiation therapy. Although there is a substantial progress in effective cancer treatment and many forms of cancer are treatable, the therapies are not always effective and often have undesired side-effects [1]. As early diagnosis is essential for successful therapy, both new diagnosis and treatment methods need to be developed. Nanotechnology, combined with other disciplines such as molecular biology and imaging technology, provides unique capabilities and enables innovative diagnosis and therapy. Furthermore, it also allows individualized treatment and treatment monitoring, taking into account patients' variability and thus their response to treatment, ensuring optimal efficacy of the applied therapy. While this technology is currently mostly applied to various types of cancer, it could soon find applications to other diseases.

2. Nanomaterials in Cancer Diagnosis

As early diagnosis is associated with positive outcome, using any type of therapy, there are many incentives for developing technologies that can detect cancer at its earliest stages. In most cases, detection of stage 1 cancers is associated with a higher than 90% 5-year survival rate [2, 3] due to availability of curative treatment.

Currently, cancer is detected using various medical tests such as blood, urine, or imaging techniques followed by biopsy. Conventional anatomical imaging techniques typically detect cancers when they are few millimeters (e.g., MRI) or centimetres (e.g., PET) in diameter, at which time they already consist of more than a million cells. Recently proposed molecular imaging aims at rectifying this disadvantage. The development of this new imaging modality became possible due to the recent progress in nanotechnology, molecular and cell biology, and imaging technologies. While molecular imaging applies to various imaging techniques such as Positron Emission Tomography (PET), computed tomography

(CT), or ultrasound, of particular interest is magnetic resonance imaging (MRI) that provides the best spatial resolution when compared to other techniques and is noninvasive or at least minimally invasive. Unfortunately, MRI has not been applied to its full potential for the diagnosis of cancer mostly because of its low specificity (false-positive rate of 10% for breast cancer) [4–8]. The lack of MRI specificity can be, however, rectified using cell markers and unique properties of paramagnetic and superparamagnetic nanoparticles (NP), which can be utilized to be detected with MRI in small quantities. Super(paramagnetic) nanoparticles when placed in the magnetic field disturb the field causing faster water proton relaxation, thus enabling detection with MRI.

Nanoparticles, typically smaller than 100 nm, have been applied to medicine [9, 10] due to their unique magnetic properties and sizes, comparable to the largest biological molecules, such as enzymes, receptors, or antibodies, that enable diagnostic, therapy as well as combined therapy and diagnostic (known as theranostics) [11, 12]. Nanoparticles with potential MRI-related medical applications comprise various materials, such as metals (gold, silver, and cobalt) or metal oxides (Fe_3O_4, TiO_2, and SiO_2).

A passive or active method can be used to deliver nanoparticles to the specific site. An example of passive application of iron-based nanoparticles is liver cancer that lacks an efficient method of early diagnosis. Current techniques, including ultrasound, CT, and MRI, detect liver tumors only when they have grown to about 5 centimeters in diameter. By that time, the cancer is especially aggressive, resisting chemotherapy, and difficult to remove surgically. Application of iron-based nanoparticles improved MRI sensitivity due to accumulation of iron in the liver caused by selective action of the hepatobiliary system (Figure 1). This type of contrast delivery does not apply, however, to most of the cancers thus targeted, and active delivery is used.

From the point of view of MRI technique, to increase MRI sensitivity, two types of contrast agents, providing positive or negative image contrast, are used. Contrast agents comprising gadolinium (Gd) or manganese (Mn) provide hyperintense T_1-weighted tumor images [13–16], while superparamagnetic nanoparticles reduce T_2 and T_2^* of surrounding water molecules, thus decreasing MR signal in T_2- and T_2^*-weighted MRI (negative image contrast) in the areas corresponding to the location of the disease [17]. Gadolinium (III), with its high electron magnetic moment, is the most common T_1 contrast agent, that provides nonspecific positive T_1 contrast.

Free Gd^{3+} is toxic ($LD_{50} = 0.2\ \text{mmol kg}^{-1}$ in mice); therefore, it is administered in the form of stable chelate complexes that prevent the release of the metal ion *in vivo* [18]. Following intravascular injection, nonspecific Gd-based compounds distribute rapidly between plasma and interstitial spaces and are ultimately eliminated through the renal route with half-lives of about 1.6 h [18]. Polyaminocarboxylate ligands, which incorporate nitrogen and oxygen donor atoms, are used to coordinate the Gd center. The Gd-based contrast agents are provided commercially by various suppliers. Accumulation of these contrast agents is solely based on differences in the vasculature between tumor and normal tissues; thus, MRI recognition of specific tumor types is not achieved. Molecular MR imaging rectifies this drawback by taking advantage of the distinctive cell properties (such as a unique pattern of protein expression) of the tumor and combines them with superparamagnetic nanoparticles enabling both sensitive and specific detection of molecular targets associated with early events in carcinogenesis [2]. To enable MR specificity, nanoparticles may be conjugated with various organic vehicles (Figure 2), for example, with single domain antibodies (sdAb) that are specific for proteins that are overexpressed on the surface of the tumor cells, in the tumor microenvironment (e.g., the extracellular matrix (ECM)), or by the tumor vasculature.

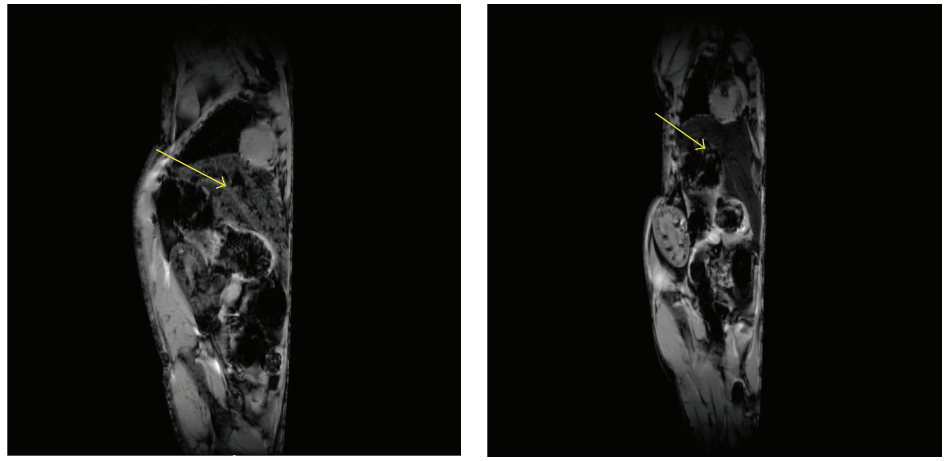
There are various corresponding receptors such as epidermal growth factor receptor (EGFR), a cell surface receptor known to be overexpressed, for example, in the triple negative (TN) breast cancers or secreted clusterin (sCLU), and a protein that is secreted into the microenvironment and that has been shown to be associated with the progression of primary to metastatic carcinoma. Insulin Growth Factor Binding Protein 7 (IGFBP-7) has been shown to be specifically overexpressed by the tumor vasculature; it can also be used as a vascular target [19, 20]. The agents against these selected targets can be developed using single domain antibodies that have been shown to specifically bind to these targets. Such a probe allows localization of the disease *in vivo*, and potentially gives insight into biological processes (e.g., angiogenesis and metastasis) which are critical to tumor development and can, therefore, be used to monitor the response of a tumor to individualized therapy. This way, treatment may be applied at a curable stage and adjusted if needed. Furthermore, MRI, in particular when combined with application of nanoparticles, has a capability in cancer staging, following up the progress of treatment, and accurate detection of lymph nodes involvement in disease [21] as showed in the recently reported detection of small and otherwise undetectable lymph node metastases in patients with prostate cancer [22, 23].

3. Therapeutic Applications of Nanoparticles

While diagnostic is a common medical application of nanoparticles, they can also be used for therapy [9, 24, 25]. Their properties offer unique interactions with biomolecules both on the surface and inside the cells, enabling significant improvement in cancer diagnosis and treatment [26]. Therefore, nanoparticles have been recently utilized by biologists, pharmacologists, and physicists, physicians as well as the pharmaceutical industry [27].

There are about 20 clinically approved nanomedicines used for treatment. An example is Abraxane, an albumin-bound form of paclitaxel with Cobalt of mean particle size of approximately 130 nm that is used to treat breast cancer [28]. Doxil, also based on Cobalt, is used for the treatment of refractory ovarian cancer and AIDS-related Kaposi's sarcoma and it consists of nanoparticles with a polyethylene glycol (PEG) coating [11, 29, 30].

A primary attribute of nanoparticles delivery systems is their potential to enhance the accumulation of anticancer agents in tumor cells as some nanoparticles passively accumulate in tumors after their intravenous administration [1, 28, 31–33]. Nanoparticles can penetrate through small



(a) (b)

Figure 1: An MR image (gradient echo, TR/TE = 100 ms/4 ms, flip angle 30°, FOV = 5.5 cm × 2.5 cm, 256 × 256) of a mouse liver obtained at 9.4T before (a) and after (b) injection of iron oxide (Nano-Ocean, USA). Decrease of MR signal within the liver (yellow arrow) is visible.

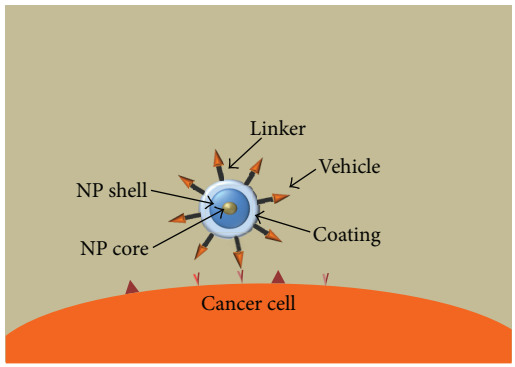


Figure 2: Schematic representation of a targeted contrast agent used for MRI approaching of the cancer cell and expressing specific proteins (modification from [19]).

capillaries and are taken up by cells, which allow efficient drug accumulation at target sites enabling also a sustained and controlled release of drugs at target sites over a period of days or even weeks [1, 28, 31–33]. In general, drug targeting by nanoparticles or nanocapsules reduces dosage, ensures the pharmaceutical effects, minimizes side-effects, and enhances drug stability [1, 34–36].

Bare nanoparticles are inherently unstable under physiological conditions; thus, they are coated with biocompatible polymers that improve colloidal stability in biological media preventing agglomeration and subsequent precipitation.

Colloidal nanoparticle systems for biomedical applications should also exhibit low toxicity and possess a long shelf life [12]. Therefore, magnetic nanoparticles are the subject of intense research focusing on their synthesis, characterization, biocompatibility, and functionalization [13, 37]. The organic coating may also provide a means for delivery of drugs or/and bioconjugation of biological vehicles (e.g., antibodies), thus enabling transportation to the specific disease site [9, 38]. A protective layer increases circulation half-life by preventing action of the immune system and allows for the addition of targeting agents. [11, 30, 39–42]. The core particle is often protected by several monolayers of inert material [9, 17], that composition depends on its application. Various research groups have studied the effect of nanoparticle coating on cellular toxicity [9]. For example, Goodman and colleagues [43] demonstrated that cationic nanoparticles were moderately toxic, while as-anionic nanoparticles were nontoxic [9, 43]. The authors found that nanoparticles functionalized with quaternary ammonium have mild effects on cell viability, while carboxy-functionalized nanoparticles do not have effects [9, 43]. Pisanic et al. [44] found that magnetic nanoparticles coated with dimercaptosuccinic acid (DMSA) were toxic to neurons in a dose-dependent manner [44] while Wilhelm and colleagues [45] have shown that DMSA coated nanoparticles are non-toxic to HeLa cells or RAW macrophages [9, 45]. The most common coatings are polyethylene glycol (PEG) [46], polyvinyl alcohol (PVA) [47], polysaccharides chitosan [48], dextran [49], carboxymethyl dextran (CMDx) [50], starch, albumin, silicones, or polyvinylpyrrolidone (PVP) [9, 51]. While the same layer might act as a biocompatible material, more often an additional layer of linker molecules is used to improve further functionalization. The linear linker molecule has reactive groups at both ends. One group is aimed at attaching the linker to the nanoparticle surface and the other is used to bind various moieties like proteins, antibodies, or fluorophores, depending on the application [17], creating a targeted contrast agent [9, 52]. The choice of material, its size, and the way in which it is coated or protected becomes of great importance in moving a nanoparticle into clinical use [11].

The most commonly used method of drug delivery is the antibody- or ligand-mediated targeting of anticancer therapeutics similarly as in molecular imaging diagnostic. The basic principle that underlies ligand-targeted therapeutics is that the selective delivery of drugs to cancer cells or tumor vasculature can be enhanced by synthesising the drugs with molecules that bind to antigens or receptors that are either

uniquely expressed or over-expressed on target cells [1, 53–56]. The use of new synthesis techniques, such as condensation reactions, allowed the incorporation of various targeting ligands to the nanoparticle shell, including EGF-related targets [11, 57, 58], transferrin [11, 59, 60], lactoferrin [11, 61], transactivating transcriptional activator [11, 62], aptamers [11, 63], and numerous other peptides such as chlorotoxin [11, 64–68]. For example, the use of the peptide sequence known as Angiopep has recently become important for the targeting of brain cancer [11, 69] as both the BBB and gliomas are known to overexpress the corresponding receptors [11, 69]. Many researchers have recently utilized various coatings to improve the drug delivery. For example, Veiseh et al. [66, 70] found that the incorporation of chlorotoxin onto functionalized Fe_3O_4 nanoparticles resulted in a significant increase in the total uptake within the brain tumors of mice after *in vivo* injection when compared with untargeted particles; Kim and coworkers found that hydrophobic drugs could be incorporated into monolayers of polyelectrolyte-coated gold nanoparticles for cellular delivery [11, 71]. Liu et al. utilized polymer-coated magnetic nanoparticles to deliver the anticancer drug epirubicin and to provide an MRI contrast agent for brain cancer [11, 72].

An example of an organic-based delivery vehicle is liposomes, which are spherical in shape and consist of a phospholipid shell that can be used to encapsulate and deliver both hydrophobic and hydrophilic drugs [11]. They are on average 100 nm in diameter [41, 73–75]. Doxorubicin was the first drug to be delivered by liposomes to brain tumors [11, 41, 74, 75]. High-density lipoprotein (HDL) nanoparticles are closely related to liposomal nanocarriers, having the stability and monodispersity of inorganic nanoparticles combined with the shielding ability of liposomes that improve circulation half-lives of therapeutics [76–78].

Nanoparticles with controllable sizes ranging from a few nanometers up to tens of nanometers are of particular interest. They are thousands of times smaller than cells and comparable with viruses, proteins, and genes. Therefore, they are able to cross biological membranes, interact closely with biomolecules enabling access to intra- and extracellular spaces thus inducing various responses in biological systems [79] and improving cancer therapy and/or diagnosis. Nanoparticles provide a means to increase transport across the BBB and/or blood-brain-tumor barrier (BBTB) and for this reason have been exploited in the treatment of brain cancer [11, 80–86]. For example, nanoparticles are promising in glioma treatment. This brain cancer is particularly difficult to treat [11, 87, 88] as neurosurgery is ineffective, while chemotherapy suffers from the inability of therapeutics to cross the blood-brain barrier (BBB). Several different types of nanoparticles have been employed as imaging and delivery agents for brain cancer treatment, including Fe_3O_4 nanoparticles [11, 42, 66, 70, 89–93], gadolinium [81, 94–96], gold [97], semiconductor quantum [QDs] [11, 58, 98], and organic-based (dendrimer, hydrogel, and polymer) nanoparticles [11, 64, 67, 68, 73, 99–101].

While nanoparticles can function as delivery vehicles with variable sizes, shapes, and surfaces that serve to increase bioavailability and specificity of cancer therapeutics, they can also allow loading of additional drugs for simultaneous multidrug delivery. The addition of imaging probes may be utilized for simultaneous diagnosis, therapy, and monitoring. Finally, toxicity of nanoparticles could also be potentially utilized to destroy the cancer cells [11, 41, 102–104].

Although not yet fully developed, methods of activation of nanoparticles after reaching the target are being investigated. An example is the use of metallic nanoparticles that can be heated with light, radiofrequency, or magnetic fields for thermal ablation of tumors [17, 43–46, 105–107]. The oscillating magnetic field can be applied after the particles reach the tissue of interest, as determined, for example, by MRI. The drug release is induced by the temperature increase generated by the magnetic nanoparticles subject to an oscillating magnetic field. This temperature increase is then utilized to stimulate a thermoresponsive polymer synthesised to the nanoparticle surface.

4. Iron-Based Nanoparticles

The inorganic nanoparticles that have been applied clinically are mainly nanoparticles based on iron oxide, Fe_3O_4, with diameters around 50 nm as these nanoparticles have been relatively well-tolerated.

The most common and the first to be applied in MRI nanoparticle is the so-called small and ultrasmall superparamagnetic iron oxide (SPIO and USPIO, resp.). SPIONs are typically monocrystalline composed of magnetite (Fe_3O_4) or maghemite (γ-Fe_2O_4) [22]. Because iron oxide has a relatively low saturation magnetization, it requires the use of large particles to achieve sufficient MRI contrast [4]. Iron oxide nanoparticles vary in size and may have different types of surface coating, which significantly affect their blood half-life, biodistribution, and uptake. The synthesis method utilized to produce SPIO nanoparticles determines the size and polydispersity of the particle population [5, 6].

Magnetic iron oxide particles have been used clinically since 1987, when they were applied for the detection of focal liver and spleen lesions with MRI. SPIOs, with hydrodynamic diameter larger than 30 nm, tend to have a short blood half-life as they are taken up by mononuclear phagocytosing system (MPS) in liver and spleen, leading to a significant MR signal loss in these tissues in T_2-weighted MR images [22, 108]. Focal liver lesions without an MPS or without an intact MPS do not show this accumulation and maintain their precontrast signal intensity [22]. Thus, SPIO-enhanced MRI shows an increase of liver-to-tumor contrast with respect to the precontrast images, allowing differential diagnosis of malignant versus benign liver lesions or metastases [14, 15, 22]. The USPIOs (<30 nm diameter) can escape the initial uptake by liver and spleen; thus, they can reach other targets that can be then indirectly detectable with MRI and thus are used as targeted contrast agents after their bioconjugation.

There are several commercially available compounds containing superparamagnetic iron oxide such as Feridex (Berlex, USA), Endorem (Guerbet, EU), and Resovist (Schering, EU, Japan). They are mostly used for liver and spleen tumors diagnosis [22]. These particles are of medium size and are coated with dextran (Feridex, Endorem) or an alkali-treated

low molecular weight carboxydextran (Resovist). Their relaxivity ($r_2 = 1/T_2$) varies [109]: 186 $mM^{-1}s^{-1}$ (Resovist, 4.0 nm core, hydrodynamic diameter 60 nm), 120 $mM^{-1}s^{-1}$ (Feridex, 4.96 nm core, hydrodynamic diameter 160 nm), and 65 $mM^{-1}s^{-1}$ (Combinex, 5.85 nm core, hydrodynamic diameter 30 nm) at 1.5 T.

Although iron oxides have been the most widely used, biomedical applications of magnetic ferrites are currently being intensely investigated. In particular, substituted magnetic spinel ferrites of the general formula MFe_2O_4 (where $M = Zn^{2+}$, Mn^{2+}, Co^{2+}, Ni^{2+}, and Mg^{2+}) offer the opportunity to fine-tune the magnetic properties of the inorganic nanoparticle core as a function of the kind of divalent ion [16]. Large magnetic moments, observed in these nanoparticles, are preferred for most applications, as they reduce the amount of nanoparticles needed to detect them with MRI. However, their toxic effects are often considerable and need to be reduced. Therefore, a balance between larger magnetic moments, nanoparticles concentration, and their biocompatibility is the goal of the researchers involved in the synthesis of clinically relevant nanoparticles [16].

5. Other Nanoparticles

As mentioned above, other than iron oxide based nanoparticles with potential clinical application in MRI and/or CT are cobalt (Co), gold (Au@Fe), and platinum (Pt@Fe). As they have much higher saturation magnetization value than that of the iron, they have much larger effect on proton relaxation ($r_1 = 7.4\,mM^{-1}s^{-1}$, $r_2 = 88\,mM^{-1}s^{-1}$ for copolymer at 1.5 T, 3.9 nm core diameter, 28 nm particle diameter [110]) providing better MR contrast than iron oxide in the same concentration and allowing smaller particle cores to be used without compromising MR sensitivity [4]. Probably the most frequently used is cobalt. While cobalt toxicity is an issue, the undesired effects of cobalt in man are difficult to evaluate, as they are also dependent on nutritional factors [111]. Many patients have taken up to 50 mg cobalt per day as treatment of refractory anemia for long periods with little or no toxicity [4]. Most cobalt drugs also contain ferrous sulfate, which may affect the amount of cobalt absorbed, since cobalt and iron share a common absorption pathway. In contrast, 10 mg cobalt/day taken by heavy beer drinkers in the 1960s may have resulted in cardiomyopathy [111], as the effect of inadequate protein intake, thiamine intake, zinc depletion, and alcohol may render the heart more sensitive to Co^{2+} toxicity [4].

As Au@Fe magnetic moment is high and it has limited reactivity, it can also be used as an MR contrast agent. There are many subtypes of gold-based nanoparticles depending on their size, shape, and physical properties. The earliest studied gold-based nanoparticles were gold nanospheres (although not exactly spherical in a strict sense). Subsequently, gold nanorods, nanoshells, and nanocages have been investigated [26]. With continued development in the synthesis techniques over the last two decades, most of these gold nanoparticles can now be produced with well-controlled size distribution.

Gold nanoparticles have recently been investigated in delivering therapeutics to the brain cancer [86, 112–114]. These nanoparticles have the advantages of relatively straightforward synthesis, easy surface functionalization, small sizes, ability to be excreted by the body and remain relatively nontoxic [11, 57, 82]. Because gold is an excellent absorber of X-rays, it was used for improved cancer therapy. The tumors could be loaded with contrast agents containing gold increasing the radiation dose within the tumor and thus reducing unwanted radiation of normal tissue [115]. Qian et al. [116] applied gold nanoparticles for *in vivo* tumor targeting and detection based on pegylated gold nanoparticles and surface-enhanced Raman scattering (SERS). Colloidal gold has been found to amplify the efficiency of Raman scattering by 14-15 orders of magnitude [116]. A gold colloid was encoded with Raman reporter molecules and covered with a layer of thiol-PEG. Approximately 1.4-1.5 $\times$ 10^4 reporter molecules were adsorbed on each 60 nm colloid gold [116].

One of the most interesting and promising biomedical applications of Au-based nanoparticles is their application for intracellular delivery vectors for drugs and genes [117, 118]. Yan et al. [119] proposed one-pot-synthesized polypeptide-conjugated Au nanoparticles for gene delivery and efficient transfection. In their approach, positively charged polypeptides were used to serve as capping agents as well as reductants eliminating the need for an external reducing agent. The resulting positively charged polypeptide-conjugated gold nanoparticles were applied for gene delivery due to prolonged (almost two weeks) and gradual intracellular uptake and transfection [119].

In addition to providing MRI contrast, gold nanoparticles may provide a suitable bimodal, CT, and MRI contrast [11, 42, 83, 120, 121]. It is worth to mention that gold nanoparticles have been examined by the USA National Institute of Standards and Technology as a potential standard for research based on nanosized particles [86, 97, 113, 114].

6. Core-Shell Nanoparticles

The very recent development in nanotechnology enabled the production of complex particles consisting of the core and shell, each made of different atoms, such as FePt@Au [109]. In principle, there are two types of core/shell nanoparticles used in imaging applications: inorganic/organic and inorganic/inorganic [122]. The most common organic shell is silica (SiO_2), while inorganic material comprises various metals. Many inorganic core-shell nanoparticles have been constructed, including Au@Ag [123], Au@Co [124], Au@Pt [125], Au@TiO_2 [126], Au@Fe_2O_3 [127], Ni@Ag [128], Fe@Ag [129], Ni@Pt [130], Co@Au [131], Fe@Pt [132], LaF_3@Eu [133] or β-$NaYF_4 : Yb^{3+}$, and Er^{3+}/β-$NaYF_4$ [134].

This development allowed new applications of nanoparticles, for example, as targeted contrast agents generating positive contrast in MRI. Standard contrast agents shortening T_2 have been developed, yet efficient targeted contrast agents shortening both T_1 and T_2 are still an area of research as the core/shell nanoparticles could provide improved tumor delineation and hyperintense tumor MRI due to shortening both T_1 and T_2, unlike standard iron-based nanoparticles that shorten mostly T_2 [43, 135–137]. These core-shell nanoparticles can be stabilized by an organic coating that can be

pegylated for the reduction of nonspecific binding and further chemically modified for subsequent bioconjugation of the biological vehicles such as antibodies, for example, against IGFBP7 used for glioma detection [19].

7. Production of Nanoparticles

A commonly used method of magnetite synthesis is the coprecipitation of iron salts in aqueous media at room temperature under basic, inert conditions [7, 8]. This relatively straightforward method results in the formation of large amounts of magnetic core clusters of about 36 nm composed of single particles around 10 nm; however, the generated clusters are very polydisperse. Difficult control of aggregation and particle size distribution are the disadvantages of the coprecipitation method. An alternative to coprecipitation is the thermal decomposition method [24, 25, 34, 38, 51, 52]. In this method, an iron oleate precursor is prepared which is then decomposed into an iron oxide at high temperature in an organic solvent. The resulting nanoparticles have narrow size distributions but unfortunately are coated with a hydrophobic layer of oleic acid. In order to obtain stable aqueous dispersions of these particles in water, OA on the surface of the particles is exchanged for another ligand [35] which not only stabilizes the particle in suspension but can also serve to covalently attach other molecules to the surface of the particle [8].

The most common synthesis methods of core/shell nanoparticles are chemical vapor deposition, laser-induced assembly, self-assembly, and colloidal aggregation [138, 139].

In the microemulsion method [140], surfactants allow the homogenization of all types of reactants, and the particles formed are capped by the surfactant molecules [141]. Thus, the size of the nanoparticles can be controlled varying a concentration of surfactant [142]. Mandal et al. [141] used glucose to control shell growth of gold or silver onto Fe_3O_4 particles upon heating of the mixture of Fe_3O_4 particles. To cover Fe_3O_4 nanoparticles with gold or silver, a modified microemulsion method has been used [141]. This method allows shell thickness of the core-shell particles to be tunable and allowed production of structures of size from 18 to 30 nm with varying proportion of Fe_3O_4 to the noble metal precursor salts [141].

Very recently a very promising method of production of 3D colloidal spheres containing various nanoparticles was proposed [143]. These multifunctional nanoparticles may be used for different applications such as multimodal imaging, remotely controlled release, targeted drug delivery, or simultaneous diagnosis and therapy [144]. This so-called template-assisted fabrication process uses porous calcium ($CaCO_3$) microspheres as a sacrificial template. This method allows easy control of the size of the spheres, flexible tuning of their biochemical and physical properties, and encapsulation of various nanoparticles. The process comprises adsorption of nanoparticles into the porous $CaCO_3$ sphere, encapsulation of polyelectrolytes, and removal of the template by cross-linking. The end product is a colloidal sphere. Using this method, Au nanoparticles and cross-linked poly-L-lysine (PLL) (P-AuNPs) [143], citrate-stabilized gold nanoparticles (C-AuNPs) [145], cetyl trimethylammonium bromide (CTAB) capped gold nanorods (GNRs) [146], and magnetic nanoparticles (γ-Fe_2O_3) were used to create 3D hybrid colloidal spheres [147].

8. Nanoparticles for Multimodal Imaging

While various imaging techniques, such as MRI, CT, Positron Emission Tomography (PET), and infrared (IR) imaging, have been used for diagnosis and treatment monitoring, each one delivers different information on disease and its location. There is no perfect imaging method, as each technique has its advantages and disadvantages. MRI provides the best soft tissue contrast but its sensitivity is low; PET is more sensitive than MRI but its spatial resolution is low; CT is fast but soft tissue contrast is low; and finally infrared imaging is fast and very sensitive but the depth of penetration is very low. Nanotechnology allowing production of multimodal contrast agents ("all in one") takes advantages of all these modalities.

Of particular interest is the recent development of rare earth upconversion nanophosphors (RE-UCNPs) [148–152] as potential contrast agents because of their optical and biochemical properties, such as sharp emission lines, long lifetimes, and nonphotoblinking. In particular, Yb^{3+} and Tm^{3+} codoped RE-UCNPs emitting at 800 nm have been used for a whole-body small-animal near-infrared imaging [153]. This technique allowed detection of only 50 cells in a whole-body mouse imaging [154]. Unfortunately, photoluminescent imaging has a low light penetration depth, but this limitation could be rectified by simultaneous application of MRI or/and CT with a contrast agent suitable for all these techniques. Therefore, Gd^{3+} was synthesised with RE-UCNPs creating magnetic-luminescent RE-UCNPs contrast agent for bimodal imaging, allowing T_1-enhanced MRI and upconversion luminescence imaging (UCL) [155]. Furthermore, to enable CT, MRI, and luminescence imaging using the same contrast, superparamagnetic nanoparticles have been synthesized with RE-UCNPs using a crosslinker anchoring method [156]. An example is $NaYF_4$: Yb, Er@Fe_3O_4@Au, which could be used for MRI, optical, and CT imaging [157]. $NaYF_4$: Yb, Tm@Fe_xO_y core-shell nanostructure was used for T_2-weighted MRI and UCL bimodal lymphatic imaging [158]. Of particular interest for multimodal contrasts may be $NaLuF_4$ because RE-UCNPs based on the $NaLuF_4$ have high UCL quantum yield [159] and high X-ray absorption coefficient. Another example of multimodal application of nanoparticles is their simultaneous utilization in high-resolution MRI and high-sensitivity PET for more accurate disease detection. The PET marker (e.g., Cu^{64}) can be added to an MR marker, creating a MRI/PET contrast agent. Furthermore, radionuclide attachment can be achieved via chelating agents.

9. Conclusions

Recent developments in nanomaterials, molecular and cellular biology, and imaging technology enabled to enhance our diagnostic and therapeutic capabilities, improving detection limits from the tissue down to the cell and even to the molecular level. We can now combine atom and biomolecular

manipulation applying quantum physics, molecular chemistry, biology, and genetics to fabricate minute synthetic structures [1, 160] and to apply them along with high-resolution noninvasive imaging technologies for diagnosis, therapy, and treatment monitoring. Current investigation of nanomaterials in animal models has offered less invasive diagnosis and induced fewer side-effects due to improved targeting, yet up to date their clinical applications have been limited. The major obstacle seems to be the long time needed for clinical trials and associated costs. Despite that nanomaterials will likely have a significant impact on patient care in the future.

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