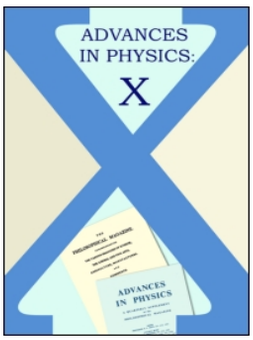

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REVIEW ARTICLE

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Nanoparticles in biomedical applications

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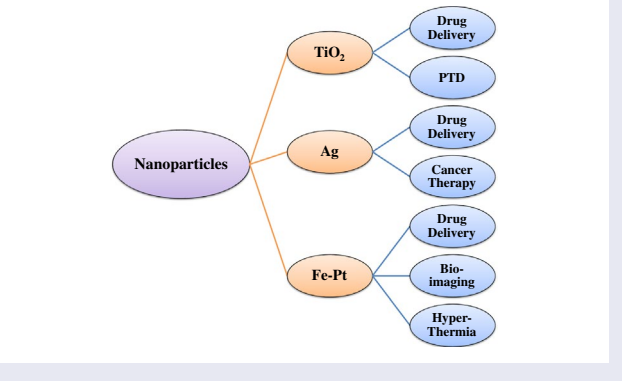
ABSTRACT

Nanoparticles are defined as solid colloidal particles ranging in size from 10 to 1000 nm. Nanoparticles offer many benefits to larger particles such as increased surface-to-volume ratio and increased magnetic properties. Over the last few years, there has been a steadily growing interest in using nanoparticles in different biomedical applications such as targeted drug delivery, hyperthermia, photoablation therapy, bioimaging and biosensors. Iron oxide nanoparticles have dominated applications, such as drug delivery, hyperthermia, bioimaging, cell labelling and gene delivery, because of their excellent properties such as chemical stability, non-toxicity, biocompatibility, high saturation magnetisation and high magnetic susceptibility. In this review, nanoparticles will be classified into four different nanosystems metallic nanoparticles, bimetallic or alloy nanoparticles, metal oxide nanoparticles and magnetic nanoparticles. This review investigates the use of nanosystems other than iron oxide nanoparticles such as metallic nanoparticles like gold (Au) and silver (Ag), bimetallic nanoparticles like iron cobalt (Fe-Co) and iron platinum (Fe-Pt) and metal oxides including titanium dioxide (TiO_2) cerium dioxide (CeO_2), silica (SiO_2) and zinc oxide (ZnO) with a focus on the lesser studied nanoparticles such as silver (Ag), iron-platinum (Fe-Pt) and titanium dioxide (TiO_2) and how their unique properties allow for their potential use in various biomedical applications.



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87.90.+y Other topics in biological and medical physics was used as there is both a biological and medical physics aspect to this paper, using different instruments and the physics behind them as well as the biological side to testing of the nanoparticles; 81.05.–t Specific materials: fabrication, treatment, testing, and analysis; 81.07.–b Nanoscale materials and structures: fabrication and characterization; 87.85.–d Biomedical engineering

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1. Introduction

Nanoparticles are defined as 'solid colloidal particles ranging in size from 10 to 1000 nm (1 μm)' [1]. Nanoparticles are used in biomedical applications as they offer many advantages to larger particles such as increased surface to volume ratio and increased magnetic properties [2]. Nanoparticles may be classified into different nanosystems. For the purpose of this review, nanoparticles will be divided into four nanosystems; metallic nanoparticles, bimetallic or alloy nanoparticles, metal oxide nanoparticles and magnetic nanoparticles.

In recent years, there has been a steadily growing interest in using these nanosystems in different biomedical applications such as targeted drug delivery, hyperthermia, photoablation therapy, bioimaging and biosensors [3,4]. A lot of literature have focused on iron oxide nanoparticles because of their superior chemical, biological and magnetic properties including chemical stability, non-toxicity, biocompatibility, high saturation magnetisation and high magnetic susceptibility [5–8]. These properties allow for its use in many biomedical applications; bioimaging [9–30,34,41,56,62], hyperthermia [20,21,31–46,55], drug delivery [47–69], cell labelling [26,70] and gene delivery [71–77]. From our most recent review, it was seen that other magnetic nanomaterials such as Fe–Co, Cu–Ni, Fe–Ni, Co–Fe_2O_4 and Mn–Fe_2O_4, nanoparticles are being investigated for use in bioimaging [78–91,109], hyperthermia [92–107,111] and drug delivery [84,85,90,101,104,106–111] as possible alternatives to iron oxide nanoparticles [4].

This review investigates other nanosystems such as metallic nanoparticles like gold (Au) [112–130] and silver (Ag) [131–154], bimetallic nanoparticles like iron cobalt (Fe–Co) [78–80,92–97,108,109] and iron platinum (Fe–Pt) [155–172] and metal oxides including titanium dioxide (TiO_2) [173–187], cerium dioxide (CeO_2) [188–194], silica (SiO_2) [195–201] and zinc oxide (ZnO) [202–205] for possible use in biomedical applications. We focus our attention on investigating the potential of metallic (Ag), bimetallic (Fe–Pt) and metal oxide (TiO_2) nanoparticles for possible use in drug delivery, hyperthermia, bioimaging, photothermal therapy, cancer therapy and biosensors [131–187].

2. Classification of nanosystems

In this section, we will classify nanoparticles into different nanosystems. For the purpose of this review, nanoparticles will be classified into four different nanosystems metallic nanoparticles, bimetallic or alloy nanoparticles, metal oxide nanoparticles and magnetic nanoparticles as shown in Figure 1. Please see Appendix 1 for further information on the cell lines mentioned during this review of the different nanosystems, as shown in Figure 1, used in biomedical applications. Some of the bimetallic, metal oxide and magnetic nanoparticles such as Fe–Pt, Cu–Ni and Fe_3O_4 may overlap. The list of metallic nanoparticles includes gold and silver. The bimetallic list includes Fe–Co, Fe–Ni, Fe–Cu, Cu–Ni and Fe–Pt

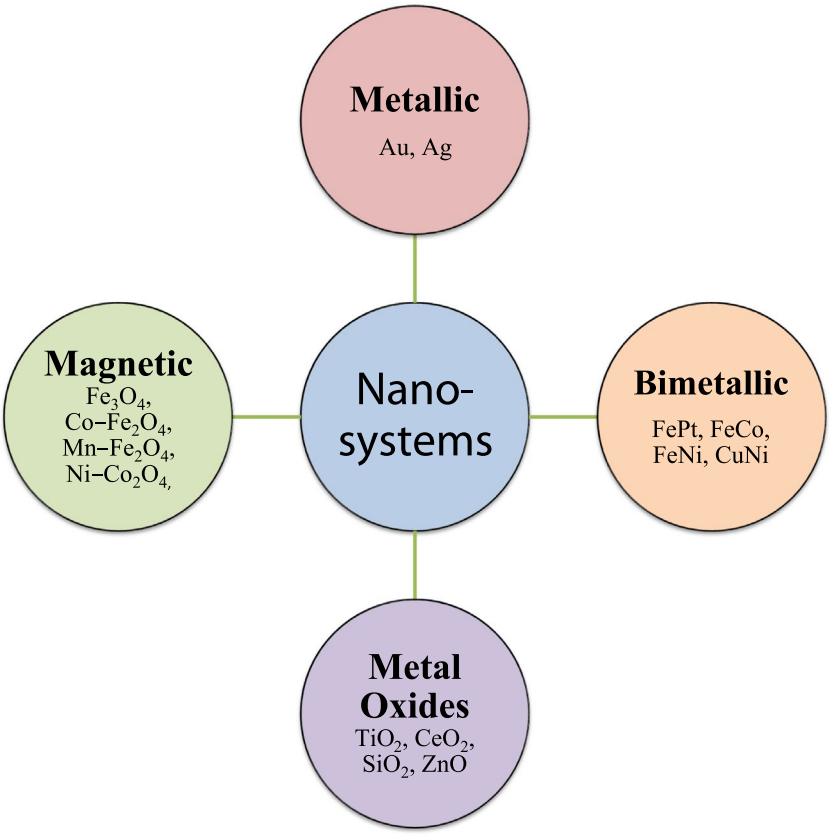

Figure 1. Schematic showing the nanosystems classification.

nanoparticles. The metal oxide nanoparticles consist of TiO_2, CeO_2, SiO_2 and ZnO. Magnetic nanoparticles are comprised of Fe_3O_4, $Co–Fe_2O_4$ and $Mn–Fe_2O_4$. These nanoparticles are the most investigated as they all possess unique properties that are essential for use in different biomedical applications such as targeted drug delivery, magnetic hyperthermia, contrast agents for bioimaging, photoablation therapy and biosensors.

2.1. Magnetic nanoparticles

Iron oxide nanoparticles are the most researched and commonly used materials for biomedical applications. Its popularity is due to unique chemical, biological and magnetic properties such as chemical stability, non-toxicity, biocompatibility, high saturation magnetisation and high magnetic susceptibility [5–8]. Iron oxide has different oxidation states including iron (II) oxide (FeO), iron (III) oxide (Fe_2O_3) and iron (II, III) oxide (Fe_3O_4). Iron (III) oxide (Fe_2O_3) has different crystalline polymorphs α-Fe_2O_3, β-Fe_2O_3, γ-Fe_2O_3 and ε-Fe_2O_3. It was found that maghemite (γ-Fe_2O_3) and magnetite (Fe_3O_4) are the most biocompatible but

magnetite (Fe_3O_4) is the most commonly used form for biomedical applications [3]. However, this form of iron oxide has a tendency to oxidise so coating with a biocompatible shell is required. Some examples of coatings include polymers [9,32,43,49,56,63,65], ceramics [17,25,59] and metals [15]. Coating with a shell offers many advantages such as it prevents agglomeration and helps with further functionalisation and conjugation to proteins, enzymes, antibodies and anticancer drugs. Iron oxide nanoparticles have been investigated for use in magnetic hyperthermia treatment [20,21,31–46,55], targeted drug delivery [47–69] and contrast agents in magnetic resonance imaging (MRI) [9–30,34,41,56,62]. The magnetic properties of iron oxide nanoparticles can be improved by doping with magnetically susceptible elements such as manganese (Mn), cobalt (Co) and nickel (Ni) [103]. Cobalt and Manganese doped ferrites are the most promising for use in biomedical applications. $CoFe_2O_4$ nanoparticles have high magneto-crystalline anisotropy, high coercivity, high Curie temperature, moderate magnetisation saturation and are chemically stable. These nanoparticles have been investigated for possible use in magnetic hyperthermia and as contrast agents for MRI [82–85,101–103]. $MnFe_2O_4$ nanoparticles were found to have high magnetisation, magnetic susceptibility and large relativities and were biocompatible. $MnFe_2O_4$ nanoparticles have been researched for possible use in magnetic hyperthermia and as possible contrast agents for MRI [86–91,103–107,111].

2.2. Metallic nanoparticles

Gold and its compounds have been used for medicinal purposes since its discovery over 5000 years ago. Gold nanoparticles use in biomedical applications is one of the most researched areas. Metallic nanoparticles such as gold (Au) possess unique electronic and optical properties as well as chemical inertness and its ability for surface functionalisation which is due to the negative charge on its surface [112–114]. Gold's unique electronic and optical properties have resulted in its use in biosensors [115–118] and bioimaging [119–123] as well as photothermal therapy [121–125]. Gold's ease at functionalisation with organic molecules allows for conjugation with ligands, antibodies or drug molecules for active or passive drug delivery [126–130]. Gold's chemical inertness allows for good biocompatibility *in vitro* and *in vivo*. Silver and its compounds like gold have been used for medicinal purposes since its discovery. Silver nanoparticles have unique physicochemical properties such as high electrical conductivity, thermal conductivity, chemical stability, catalytic activity, antibacterial and enhanced optical properties [131,132]. These properties have led to the use of silver nanoparticles in electronic, photonic, antimicrobial and disinfectant applications [133–143]. Because of silver nanoparticles extraordinary antimicrobial activity it is mainly used in the medical industry for textiles, wound dressings and device coatings. However, the use of silver nanoparticles in biomedical applications such as biosensors [133–135] photothermal therapy and drug delivery [144–154] is increasing and will be discussed in Section 4.

2.3. Bimetallic or alloy nanoparticles

Iron cobalt (Fe–Co) nanoparticles also have good magnetic properties such as superparamagnetism, high Curie temperature and high saturation magnetisation; however, they oxidise easily and their biocompatibility comes into question. To overcome this, Fe–Co nanoparticles are generally coated with a biocompatible material. Due to their high saturation magnetisation, Fe–Co nanoparticles have been utilised in biomedical applications such as contrast agents for MRI [78–80] and magnetic hyperthermia [92–97]. Iron nickel (Fe–Ni) nanoparticles have a high Curie temperature and high saturation magnetisation properties and are mainly used as contrast agents for MRI [81]. Copper nickel (Cu–Ni) nanoparticles show good Curie temperatures and magnetic properties with their main use being for magnetic hyperthermia [98–100]. Bimetallic nanoparticles such as iron platinum (Fe–Pt) possess unique chemical and magnetic properties such as chemical stability, superparamagnetisation, high Curie temperature, high saturation magnetisation and high X-ray absorption [155–158]. These properties make them attractive materials for use in hyperthermia treatment [159,160], MRI contrast agents [161–166], drug delivery [167–171] and biosensors [172] which will be discussed in more detail in Section 4.

2.4. Metal oxide nanoparticles

TiO_2 is a widely studied material and has important uses in many photocatalytic and photovoltaic devices as well as in paint, food colouring, toothpaste and cosmetics. TiO_2 nanoparticles have many unique properties such as biocompatibility, chemical stability and optical properties [173]. It is because of these properties that there has been a recent increase in the use of TiO_2 nanoparticles in biomedical applications such as drug delivery [174–179], bioimaging [175], photoablation therapy [180–185] and biosensors [186,187], which will be discussed further in Section 4. Other metal oxide nanoparticles that are gaining interest in biomedical applications are cerium oxide (CeO_2) nanoparticles or nanoceria. Nanoceria has a unique property of being able to switch between oxidation states [188–190]. Cerium oxide nanoparticles have many defects on the surface of the nanoparticle; these defects are mainly oxygen vacancies which result in a mixed valance of cerium (IV) and cerium (III) oxidation states which coexist on the surface. This results in a redox couple which is the reason for nanoceria's catalytic activity. This has led to an increased interest in nanoceria as a potential biological antioxidant. Nanoceria has been used in biomedical applications as a biosensor and as an anticancer agent [191–195]. The use of porous silica (SiO_2) nanoparticles in biomedical applications is increasing due to its unique properties including large specific surface area, pore volume, controllable particle size and good biocompatibility. It is due to these properties that mesoporous silica nanoparticles have been investigated for potential use in drug delivery and biosensors [196–202]. Recently, the use of zinc

oxide (ZnO) in biomedical applications such as drug delivery and bioimaging has been increasing. However, the surface of ZnO nanoparticles needs to be modified to protect them in biological systems as they can be dissolved easily in water and acidic solutions. Also to use ZnO nanoparticles for fluorescence in imaging, the nanoparticles need to be doped as the ZnO bandwidth is in the UV region and UV light cannot penetrate tissue and is also harmful to cells and tissue [203–206].

3. Biomedical applications

3.1. Introduction

In this section, a brief review of the principles of each application is given and the use of certain nanoparticles in these applications is reviewed in Section 4. Figure 2 shows a schematic of the biomedical applications that will be discussed in this section.

Targeted drug delivery is an important biomedical application that aims to deliver anticancer drugs to the specific site of the tumour and avoid damage to

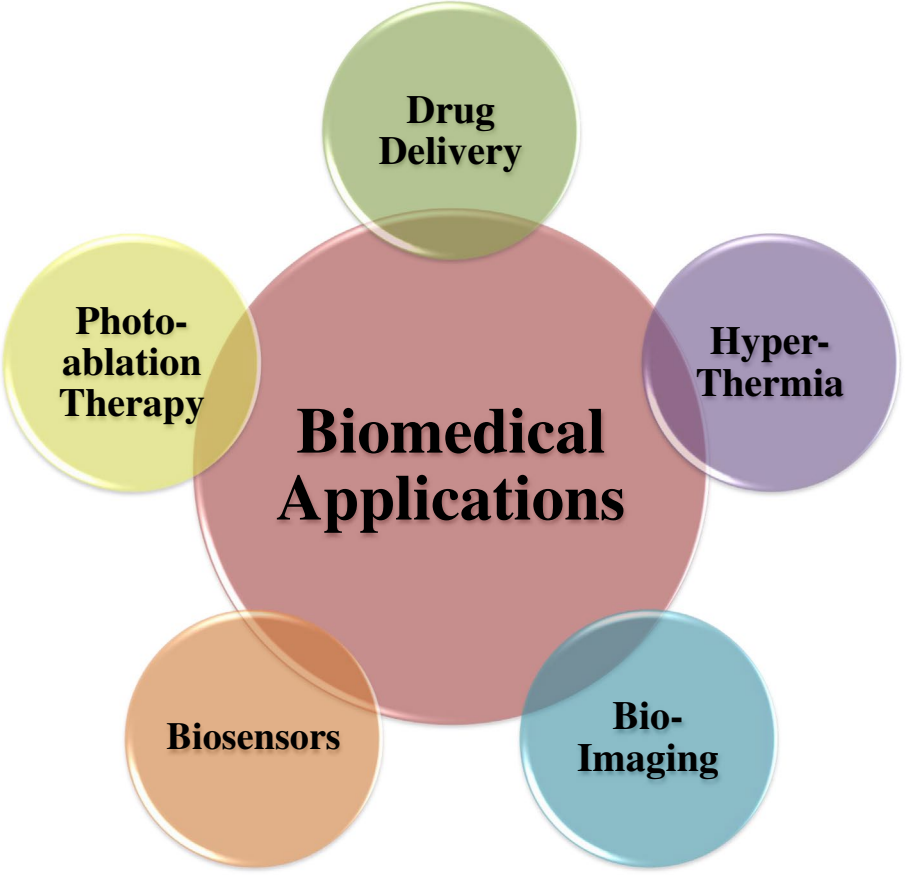

Figure 2. Schematic showing some of the biomedical applications of nanoparticles.

surrounding healthy cells. Currently, iron oxide nanoparticles are the main source of magnetic materials being used to deliver anticancer drugs to target specific areas [207–211]. In Section 4, we review the use of other nanosystems specifically Ag, TiO_2 and Fe–Pt nanoparticles for their potential use in targeted drug delivery. ZnO and Au nanoparticles have also been investigated for use in targeted drug delivery.

Another important biomedical application of nanoparticles is magnetic hyperthermia treatment. Magnetic hyperthermia treatment treats tumours by heating them to above 42 °C to destroy the cancerous cells. The benefit of this technique over chemotherapy is that it specifically targets the tumour and does not damage the surrounding healthy tissue. Again iron oxide (Fe_3O_4) nanoparticles are the main material that is currently used for this treatment [207–210,212–215]. However, other nanosystems such as bimetallic nanoparticles Fe–Co and Cu–Ni and magnetic nanoparticles such as Co–Fe_2O_4, Mn–Fe_2O_4 and Ni–Co_2O_4 have also been investigated. In Section 4, we investigate the possible use of Fe–Pt nanoparticles in hyperthermia treatment. The use of magnetic nanoparticles as contrast agents for bioimaging techniques such as MRI and computed tomography is another important biomedical application of nanoparticles [207–211,216–219]. For MRI, iron oxide nanoparticles are the main alternative being investigated to replace gadolinium chelates which are currently in use. Other magnetic nanoparticles that are being investigated as possible contrast agents include Fe–Co, Fe–Ni, Fe–Pt, $MnFe_2O_4$ and $CoFe_2O_4$. In Section 4, we investigate in more detail the use of Fe–Pt nanoparticles as contrast agents for MRI. Photoablation therapy uses light sensitive materials to destroy diseased tissue such as cancerous tumours. Different nanoparticles such as Au, Ag, Fe–Pt, ZnO and TiO_2 have been investigated for possible use in this therapy. The photodynamic use of TiO_2 nanoparticles is discussed in Section 4 [114,173,220–223]. Biosensors have emerged as an important biomedical application for sensing a variety of biomolecules. A variety of nanoparticles, such as Au, Fe–Pt, CeO_2 and TiO_2, have been investigated for possible use in biosensors.

3.2. Targeted drug delivery

Chemotherapy depends on the circulatory system to transport anticancer drugs to the tumour. There are negative side effects of this treatment such as non-specificity and toxicity of the drug, whereby the drugs attack healthy cells and organs as well as the cancerous cells. Therefore, targeted drug delivery is being developed as one alternative to chemotherapy treatment. The aim of targeted drug delivery is to direct the drug to the specific area where the tumour is located and thereby increasing the amount of drug delivered at the tumour site and reducing the side effects.

In targeted drug delivery, magnetic nanoparticles are used to deliver the drug to its specific location. Generally, the magnetic nanoparticles are coated with a biocompatible layer, such as gold or polymers, this is done to functionalise the

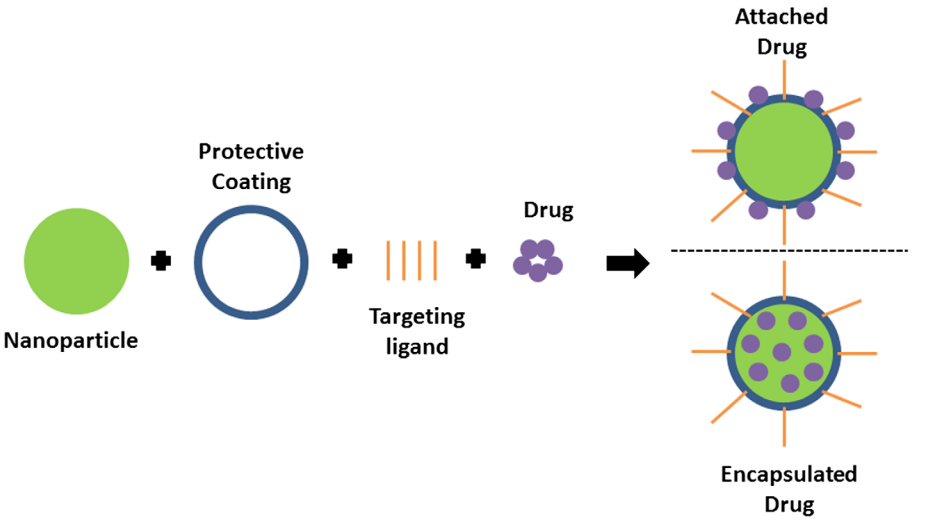

Figure 3. Schematic of drug loading options in targeted drug delivery.

nanoparticles so that the anticancer drug can either be conjugated to the surface or encapsulated in the nanoparticle as shown in Figure 3. Once the drug/nanoparticle complex is administered, an external magnetic field is used to guide the complex to the specific tumour site. The drug is released by enzyme activity or by changes in pH, temperature or osmolality [207–211].

3.3. Magnetic hyperthermia

Hyperthermia is a therapeutic technique whereby heat is applied to destroy cancerous cells and tissue. The temperature of the infected or diseased area is raised to 41–46 °C to kill the cancerous cells without damaging the healthy cells. Cancerous cells have a higher sensitivity to temperature than healthy cells. Cell apoptosis will occur when the cancerous cells are heated to 41–46 °C, this is called hyperthermic effect. Necrosis will occur if the cells are heated to above 46–48 °C, referred to as thermoablation. Hyperthermia treatment is used in combination with radiotherapy and chemotherapy to treat cancerous cells.

There are three different types of hyperthermia treatment local, regional and whole body hyperthermia. In local hyperthermia treatment, heat is applied to a small area which can be done using different techniques such as radio frequency, microwave and ultrasound. These methods are used to supply energy to raise the temperature of the tumour. Magnetic nanoparticles can also be used in local hyperthermia treatment. Regional hyperthermia is generally used to treat large tissue areas. In this treatment, external devices are used to heat an organ or limb. Whole body hyperthermia is often used to treat metastatic cancer that has spreads throughout the body. Local hyperthermia treatment is the main type of hyperthermia that will be discussed here. For local hyperthermia treatment, magnetic nanoparticles can be delivered to

the tumour in four possible ways arterial injection, direct injection, *in situ* implant formation and active targeting. Arterial injection requires injecting the fluid containing the magnetic nanoparticles into the tumours arterial supply. Direct injection involves directly injecting the fluid containing the magnetic particles into the tumour this method is the most commonly used. *In situ* implant formation entails using injectable formulations that form gels such as hydrogels (chitosan and sodium alginate) and organogels (Poly (ethylene-co-vinyl alcohol and cellulose acetate) to entrap magnetic particles into tumours. Active targeting is another method of delivering magnetic nanoparticles to the tumour site. It generally involves coating the magnetic nanoparticles with a tumour-specific antibody and injecting into the bloodstream. The antibodies are tumour specific and will bind to the target site.

Magnetic fluid hyperthermia is based on the principle of converting electromagnetic energy into heat. The magnetic nanoparticles are distributed around the target site and an alternating magnetic field is applied. This alternating magnetic field supplies energy which helps the magnetic moments in the particles to overcome the reorientation energy barrier. Energy is dissipated when the moments in the particles relax to an equilibrium state. This then results in the heating of the particles by Brownian rotation or Neél relaxation [207–210,212–214]. Brownian rotation is a result of rotation of the nanoparticles and is defined by:

$$\tau B = \frac{3\eta VH}{kT} \tag{1}$$

where τ_B is the Brownian relaxation time, η is the viscosity, V_H is the hydrodynamic volume of the particle, k is Boltzmann constant and T is temperature. Neél relaxation is a result of rotation of magnetic moments within the nanoparticles and is defined by:

$$\tau N = \tau_0 e \frac{KV_M}{kT} \tag{2}$$

where τ_N is the Neél relaxation time, τ_0 is 10^{-9} seconds, K is anisotropy constant and V_M is the volume of the particle. If both relaxations occur at the same time this is defined by:

$$\tau = \frac{\tau_B \tau_N}{\tau_B + \tau_N} \tag{3}$$

τ is the relaxation time if both effects occur at the same time. The relaxation times are dependent on the nanoparticles size, the larger the particles the larger the Brownian and Neél relaxation time constant will be. The heat generated by magnetic nanoparticles is quantified in terms of specific absorption rate (SAR):

$$\text{SAR} = C\frac{\Delta T}{\Delta t} \tag{4}$$

where C is the specific heat capacity of the sample and $\Delta T/\Delta t$ is the rate of temperature increase [215].

3.4. Bioimaging

There are different bioimaging techniques such as MRI, computed tomography (CT), positron emission tomography (PET) and ultrasound that are used for the detection and diagnosis of diseases. These techniques are non-invasive and some can produce high-resolution images of internal organs. Contrast agents are generally used in these bioimaging techniques in order to identify the organ or tissue of interest as well as identifying healthy tissue from diseased tissue. The main issue with the current contrasting agents in use for MRI and CT imaging is the toxicity, low retention time and low imaging time. In order to improve the imaging time and increase the biocompatibility of contrast agents, different compounds such as core–shell nanoparticles have been investigated as possible contrasting agents as they can offer an increased biocompatibility and imaging time [207–211,216–219].

MRI is based on the principle of nuclear magnetic resonance and radio frequency pulses. Certain atomic nuclei possess a nuclear spin and hence a permanent magnetic dipole moment. Several atoms possess net nuclear spin such as hydrogen (H), helium (He), carbon (C), oxygen (O), sodium (Na), phosphorus (P) and xenon (Xe). However, hydrogen atoms are the most utilised as they are widely abundant in biological tissue. The human body is largely composed of water molecules. These water molecules contain two hydrogen protons. When the nuclei of these protons are exposed to a static magnetic field, the spins will either align with (parallel) or against (anti-parallel) the magnetic field. The population difference between parallel and anti-parallel protons is determined by the difference in energy between the two states. This is determined by:

$$\Delta E = \frac{\gamma h B_0}{2\pi} \tag{5}$$

where γ is proton gyromagnetic ratio which varies for different nuclei, B_0 is the external field and h is Planck's constant. During irradiation from a resonant radiofrequency (RF) wave, at a specified frequency called Larmor frequency, the nuclei absorb electromagnetic energy and are excited to an anti-parallel state. When this radiofrequency is removed the nuclei relax to their initial, lower energy state which is termed relaxation.

There are two relaxation processes longitudinal or T_1 relaxation and transverse or T_2 relaxation. Longitudinal relaxation or T_1 relaxation is also known as spin-lattice relaxation. It is the process by which the net longitudinal magnetisation returns to its initial maximum value parallel to the magnetic field and is described by the following equation;

$$M_z = M_{z,0}\left(1 - e^{-\frac{t}{T_1}}\right) \tag{6}$$

where $M_{z,0}$ is the magnetisation in equilibrium state and T_1 is defined as the time for M_z to reach 63% of the original magnetisation after RF pulse is applied. Transverse relaxation or T_2 relaxation is also known as spin–spin relaxation. T_2 relaxation is the process by which transverse components of magnetisation decay or dephase and is described by the following equation:

$$M_{xy} = M_{xy,0}\left(e\left(-\frac{t}{T_2}\right)\right) \tag{7}$$

where M_{xy} is the decay of magnetisation, $M_{xy,0}$ is the initial transverse magnetisation and T_2 is the time for transversal magnetisation to drop to 37%. The T_1 relaxation process depends on magnetic field strength. However, the T_2 relaxation process is independent of magnetic field strength but depends on magnetic dipole–dipole moments, field inhomogeneities and proton diffusion constant. Generally, T_2 relaxation time is shorter than T_1 relaxation time.

The purpose of contrast agents in MRI is to improve the visibility of internal organs and distinguish healthy tissue from diseased tissue by shortening relaxation times. Relaxivity is the ability of a contrast agent to enhance the proton relaxation rate and is defined in terms of:

$$R_1 = \frac{1}{T_1} \propto r_1 \times c \tag{8}$$

$$R_2 = \frac{1}{T_2} \propto r_2 \times c \tag{9}$$

where R_1 and R_2 are the relaxation rates, T_1 and T_2 are the longitudinal and transverse relaxation times, r_1 and r_2 are the relaxivity constants and c is the concentration of contrast agents [216–219].

3.5. Photoablation therapy: photodynamic and photothermal therapy

Photoablation therapy is classified into photodynamic therapy (PDT) and photothermal therapy. PDT uses non-toxic light sensitive compounds called photosensitisers and upon exposure to light, at a certain wavelength, these compounds become toxic. This therapy is mainly used to target diseased cells such as cancer. In the PDT process once the photosensitisers, such as TiO_2 nanoparticles, are exposed to light at a specific wavelength, photo-induced electrons and holes are created. The photo-induced electrons and holes can further react with hydroxyl ions or water and can form oxidative radicals in the form of reactive oxygen species (ROS) and singlet oxygen. The production of these species leads to inevitable cell

death. Photothermal therapy uses a near infrared (NIR) light source to irradiate tumour cells. This light energy can be converted to heat energy which can cause hyperthermia to occur resulting in cell death. TiO_2 has many attractive properties such as biocompatibility, chemical stability and photocatalytic activity. It is these properties especially its photocatalytic activity that make it an attractive species for use in photothermal therapy [114,173,220–223].

Figure 4 shows a schematic of the photocatalytic process for TiO_2. The photocatalytic process for TiO_2 has three steps excitation, diffusion and surface transfer. In the first step, the nanoparticles absorb photons from a light source. This energy is enough to overcome the band gap and promote the electron into the conduction band. This leaves vacancies or holes in the valance band. The holes and electrons

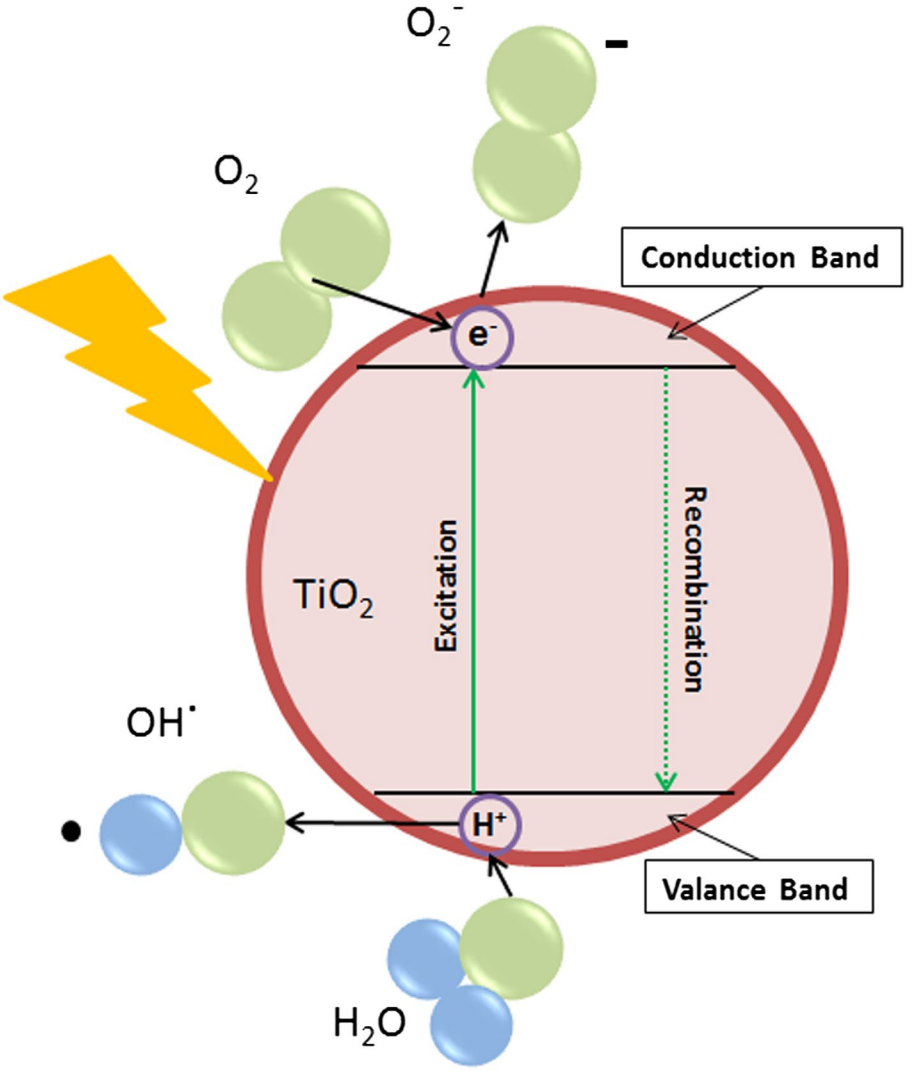

Figure 4. Schematic showing the photocatalytic process of TiO_2 nanoparticles.

then diffuse to the surface of the photocatalyst. The last step in this photocatalytic reaction is the production of chemical reactions on the surface. The creation of holes and electrons results in these reactions. The holes can react with absorbed surface water and produce hydroxyl radicals, while the electrons combine with oxygen to form superoxide radical. Figure 4 depicts the photocatalytic reaction of TiO_2 [173].

3.6. Biosensors

A biosensor is an analytical device that is used for analysing biological samples. It converts a chemical, biological or biochemical response into an electrical signal. A biosensor contains three essential components (1) bioelement or bioreceptor, which are generally made up of enzymes, nucleic acids, antibodies, cells or tissues (2) the transducer which can be electrochemical, optical, electronic, piezoelectric, pyroelectric or gravimetric and (3) the electronic unit which contains the amplifier, processor and display. Figure 5 shows a schematic of these components. The bioreceptor recognises the target analyte/substrate of interest, the transducer then transforms the resulting signal into an electrical signal that is more easily quantified. Nanoparticles can be used as bioreceptors once coated with a bioresponsive shell. Biosensors are utilised in many different areas including environmental, bio/pharmaceutical, food and medical industries [173,210].

Figure 6 shows a typical schematic of a biosensor. As mentioned previously a typical biosensor is composed of three main parts the electronic system, which contains the signal amplifier, processor and display unit, the transducer, which converts the reaction of the sample analyte and bioreceptor into an electrical signal and a bioreceptor, which is composed of a biological substance which targets and or binds to a specific compound. The transducer used in the biosensor depends on the reaction that is generated between the sample and the bioreceptor. Electrochemical biosensors such as amperometric sensors detect changes in current due to oxidation/reduction reactions. Potentiometric sensors can detect changes in charge distribution. Optical biosensors can be colorimetric which

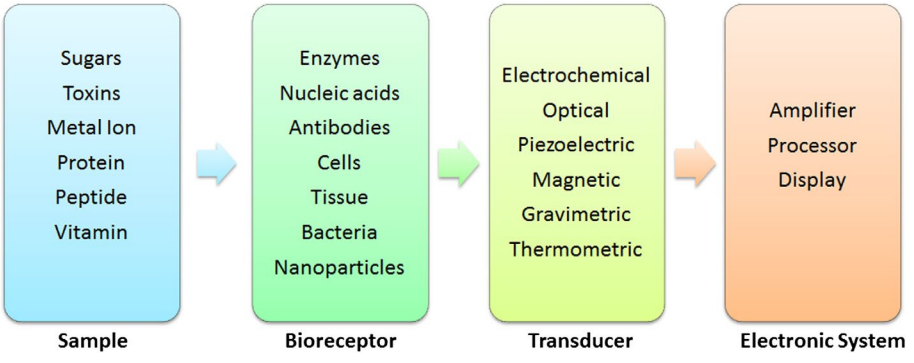

Figure 5. Schematic showing the essential components of a biosensor.

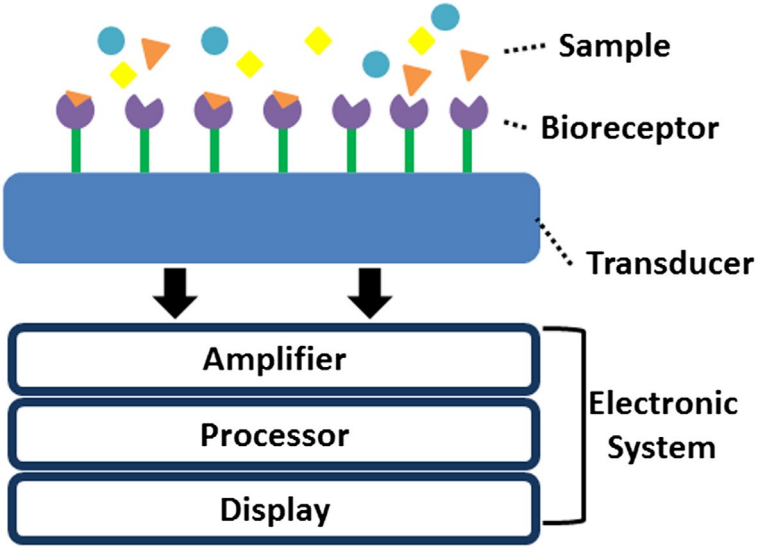

Figure 6. Schematic of a typical biosensor.

detect changes in light adsorption or photometric which detect changes in photon output. Piezoelectric sensors can detect changes in mass.

4. Biomedical applications of metallic, bimetallic and metal oxide nanoparticles

4.1. Metallic nanoparticles

4.1.1. Introduction

Silver and silver compounds have been widely used throughout history for various different applications from utensils, jewellery and currency to medicinal purposes. Silver and silver compounds were found to have healing and antidisease properties and were used to fight infection during First World War. However with the development of antibiotics, the use of silver and silver compounds as anti-infection agents faded.

The advancement in science and engineering has led to the development of nanoparticles. Silver nanoparticles or nanosilver was found to possess unique physical, chemical and biological properties when compared to the macro-sized silver particles. Silver nanoparticles were found to have high electrical conductivity, high thermal conductivity, chemical stability, catalytic activity and enhanced Raman scattering. Silver nanoparticles were also found to exhibit antibacterial, antifungal, antiviral and anti-inflammatory properties. It is because of these unique properties that nanosilver has attracted interest for use in the textile industry (clothing, underwear, socks) and food industry (food containers, refrigerator surfaces and chopping boards) as well as in medical applications such as wound dressings,

surgical instruments and bone prostheses. However, the use of nanosilver in textiles is very much discouraged, due to environmental issues. The use of silver nanoparticles in biomedical applications such as drug delivery and cancer therapy will be discussed in this section [131,132].

4.1.2. Use of silver nanoparticles for drug delivery and as cancer therapy

Research has shown the emergence of the use of silver nanoparticles in different biomedical fields such as drug delivery, diagnostics and anticancer agents. The use of colloidal silver as an anticancer agent on human breast cancer cells was investigated by Franco-Molina et al. [146]. MCF-7 human breast cancer cells were grown and different concentrations of colloidal silver nanoparticles were used to determine if a cytotoxic effect had occurred. The trypan blue exclusion method, which is a vital stain used to colour dead cells, was used to determine cell viability. The type of cell death was determined by detection of mono-oligonucleosomes, which are protein (histone) associated DNA fragments. The results showed that colloidal silver had a cytotoxic effect on human breast cancer cell line which was dose dependent. Cell death was determined to be by apoptosis with no effect to the normal cells. It was determined that colloidal silver could be used as an anticancer agent [146]. Sanpui et al. [147] developed a silver nanoparticle–chitosan nanocarrier and examined the cytotoxic effect this nanocarrier had on human colon cancer cell lines. HT 29 colon cancer cell lines were used for this study. Low concentration silver nanoparticle–chitosan nanocarriers were prepared in phosphate buffer solution (PBS) and the required volume was added to the cell cultures and incubated for 24 h. After treatment with silver nanoparticle–chitosan nanocarriers, the cells were examined by morphological (fluorescence and scanning electron microscopy) and biochemical (cell viability assay and flow cytometry) analysis to determine if cell apoptosis occurred. The results showed that low concentration silver nanoparticles–chitosan nanocarriers induced cell apoptosis in HT 29 colon cancer cells indicating its potential use in cancer therapy [147].

The use of modified nanosilver as treatment for multi-drug resistant (MDR) cancer was studied by Liu et al. [148]. MDR cancer is a major issue in the treatment of the disease as the cancer cells can survive the chemotherapy treatment. Both *in vitro* and *in vivo* studies were carried out to investigate the antitumour effect of both silver nanoparticles and modified silver nanoparticles. The silver nanoparticles were modified using TAT which is a cell penetrating peptide. The silver nanoparticles were mixed with thiol-containing TAT and the mixture was incubated for 2 h 30 min at 37 °C. Human epithelial colorectal adenocarcinoma (Caco-2), a colon cancer cell line, was used to study cellular uptake of both silver nanoparticles and modified silver nanoparticles. The inhibition activity of silver nanoparticles, modified silver nanoparticles and positive control (doxorubicin) was studied *in vitro* against skin (B16), cervical (HeLa) and breast (MCF-7 and MCF-7/ADR) cancer cell lines and were analysed using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. MTT assay is a colourimetric

assay that is used to determine cell metabolic activity. *In vivo* studies were carried out on female mice, B16 melanoma (skin cancer) cells were implanted into the mice. Once the tumour reached a certain size it was treated with silver nanoparticles, modified silver nanoparticles and positive control (doxorubicin) by injection. The results showed that enhanced cellular uptake was from the modified silver nanoparticles. It was also shown that the antitumour effect of nanosilver was concentration dependent. The *in vitro* study showed that both silver nanoparticles and modified silver nanoparticles were able to inhibit proliferation of cell lines. The *in vivo* studies showed that TAT-modified silver nanoparticles were able to inhibit tumour growth. This study shows the possible use of TAT-nanosilver in MDR cancer treatment [148]. Guo et al. [149] are investigating the cytotoxic effect that silver nanoparticles have on acute myeloid leukeamia (AML) which is type of cancer of the white blood cells in bone marrow. In this study, Polyvinylpyrrolidone (PVP)-coated silver nanoparticles of three different sizes were produced using an electrochemical method. The biological effect of these nanoparticles on different cell lines and clinical isolates was investigated. Six different AML cell lines were used in this study they included SHI-1, THP-1, DMAI, NB-4, HL-60 and HEL cell lines. Bone marrow from AML patients and healthy donors was also investigated. The effect of silver nanoparticles on cell viability, cell apoptosis, mitochondrial damage, generation of ROS and DNA damage was investigated. The results showed PVP-coated silver nanoparticles had an anti-leukaemia effect against AML cell lines and isolates. It was found that cell viability reduced with the generation of ROS and silver ions which led to DNA damage and cell apoptosis. This cytotoxic effect was stronger against the AML cells than non AML cells. These results suggest that PVP-coated silver nanoparticles could play a significant role in AML treatment [149].

The cytotoxic effect of biologically synthesised silver nanoparticles on human breast cancer cells was researched by Gurunathan et al. [150]. The silver nanoparticles were produced via green synthesis using a culture supernatant of Bacillus funiculus. The MDA-MB-231 human breast cancer cell line was used in this study. The toxicity of the silver nanoparticles to the cells was determined by cell viability, metabolic activity and oxidative stress. The results showed that cell viability was reduced and membrane integrity was compromised, these are concentration dependant. The activation of lactate dehydrogenase (LDH) and capase-3 and ROS generation resulted in cell apoptosis. The results are promising and may have potential as an alternative therapeutic agent for breast cancer therapy [150]. Govindarju et al. [150] explored the effect that silver nanoparticles produced via a green synthesis method on cancer cells. The silver nanoparticles were biosynthesised by reduction of silver nitrate using alginate extract. Acute myeloblastic leukemia (HL60) and cervical cancer (HeLa) cell lines were used to study the cytotoxicity effect of silver nanoparticles. The cells and silver nanoparticles were incubated for 5 days after which the cell viability was determined via MTT assay. Other experiments carried out to determine the cytotoxic effect of

silver nanoparticles included DNA fragmentation, lipid peroxidation and apoptosis. The results showed that cell death occurred due to apoptosis. Microscopy studies showed the endocytosis of silver nanoparticles into the nucleus of the cell which caused DNA damaged and ultimately led to apoptosis. These findings show potential for silver nanoparticles to be used in cancer therapy [151].

The use of silver nanoparticles as a drug delivery system to effectively deliver simultaneously both doxorubicin and alendronate to cervical cancer cells (HeLa) was investigated by Benyettou et al. [152]. Doxorubicin is a bacterial antibiotic often used to treat cancer. Alendronate is a powerful biophosphonate, biophosphonates are drugs that are used to slow and or stop the process that dissolves bone tissue. Biophosphonates are believed to reduce fractures and pain in people with specific types of cancer. The silver nanoparticles are coated with alendronate molecules which are fixed via chelating bisphosphonate moieties. The ammonium site is then free for drug attachment. Both doxorubicin and Rhodamine B were used to test the toxicity and cell permeability of the silver nanoparticle drug-based system. The cellular uptake results showed that Rhodamine B conjugated nanoparticles permeate the cells via macropinocytosis and endocytosis. It was also found that doxorubicin modified nanoparticles were successfully delivered to HeLa cells and had a greater anticancer activity than doxorubicin by itself or alendronate. Other drugs can be conjugated to the alendronate-coated silver nanoparticles and can become an alternative route for drug delivery to cancerous cells [152].

4.2. Bimetallic or metal alloy nanoparticles

4.2.1. Introduction

Fe–Pt nanoparticles have gained increasing attention among researchers for possible applications in biomedicine as they possess unique magnetic and chemical properties such as superparamagnetism, high coercivity, chemical stability, oxidation resistance and biocompatibility [155–158]. It is due to these properties that research for the potential uses of Fe–Pt nanoparticles in biomedical applications such hyperthermia [159,160] as contrast agents for MRI [161–166], drug delivery/cancer therapy [167–171] and biosensors [172] has increased. In this review, we will discuss the use of Fe–Pt nanoparticles in targeted drug delivery, cancer therapy, MRI contrast agents as well as its possible use in magnetic hyperthermia.

4.2.2. Fe–Pt nanoparticles as contrast agents in MRI and computed tomography (CT)

Yang et al. [163] explored the use of Fe–Pt nanoparticles as possible contrast agents for MRI. Amphiphilic Fe–Pt nanoparticles, which contain both hydrophilic and lipophilic properties, were prepared by high-temperature pyrolysis in tetraethylene glycol (TEG) medium with oleic acid (OA) as a surfactant. Cell viability studies were carried out on cervical cancer (HeLa) cell lines with these nanoparticles to determine if they are toxic. Magnetic properties such as saturation

magnetisation (M_s) and transverse relaxation time (T_2) were also investigated. The MTT assay and transmission electron microscopy (TEM) results showed that the amphiphilic Fe–Pt nanoparticles were biocompatible and no cytotoxic effect was observed. Magnetic Resonance (MR) signal enhancement studies showed clear contrast from the background. It was concluded that amphiphilic Fe–Pt nanoparticles could be potentially used as a T_2 contrast agent for MRI [163].

The use of Fe–Pt nanoparticles as contrast agents for both computed tomography (CT) and MRI was studied by Chou et al. [164]. Fe–Pt nanoparticles with three different diameters were synthesised via a high-temperature polyol method which is the synthesis of metal-containing compounds in poly (ethylene glycol), and the nanoparticles were surface modified with cysteamine. Some nanoparticles were then conjugated to anti-Her2 antibody. Both *in vitro* and *in vivo* experiments were also carried out to determine cytotoxicity, haemolysis and biodistribution of the nanoparticles. *In vitro* cytotoxicity experiments were carried out using human oral epidermoid carcinoma (OECM1) cell lines which is a form of oral cancer, Vero cell lines which are kidney cancer cell lines from a monkey and MBT2 cell lines which are from a mouse bladder. Haemolysis experiments were carried using human blood from a healthy donor. The biocompatibility results showed that no cytotoxic effect was observed and haemolysis results showed that no significant haemolysis occurred. Biodistribution experiments were performed using C3H/HeN mice and the nanoparticles were injected via tail vein and monitored for varying times. The results showed that most of the nanoparticles are cleared from all major organs with 1 week. *In vitro* CT and MRI imaging experiments were also carried out using the cysteamine-capped Fe–Pt nanoparticles to examine T_1 and T_2 relaxations. The results showed that Fe–Pt nanoparticles enhanced the shortening of T_2 relaxation. *In vitro* and *In vivo* experiments were also carried out using the Fe–Pt nanoparticles conjugated to anti-Her2 antibody. The results from this experiment showed that the conjugated nanoparticles can bind to a specific site as well as enhance the contrast. Fe–Pt nanoparticles have the potential to be used as contrast agents in CT and MRI imaging [164].

Lai et al. [165] researched the use of Fe–Pt nanoparticles for fluorescence and MRI. Fe–Pt nanoparticles were synthesised via high-temperature chemical reduction. The nanoparticles were then coated with silica using a microemulsion method to improve biocompatibility and bioconjugation. This made it easier to incorporate fluorescent dye fluorescein-isothiocyanate (FITC) into the silica shell. The cytotoxicity of Fe–Pt and Fe–Pt/SiO_2/FITC nanoparticles was determined by MTT assay using human cervical cancer cell line (HeLa). No cytotoxic effect was observed for the silica-coated nanoparticles suggesting that the coating suppresses any toxicity from Fe–Pt nanoparticles. Confocal laser microscopy was used to examine intracellular localisation of Fe–Pt/SiO_2/FITC nanoparticles in HeLa cells after staining with a red fluorescent dye. The results showed that after 12-h incubation fluorescence was observed. These results showed the potential use of Fe–Pt/SiO_2/FITC nanoparticles for dual fluorescence and MR imaging

[165]. The possible use of Fe–Pt nanoparticles as contrast agents for diagnosis of brain tumours was investigated by Liang et al. [166]. Fe–Pt nanoparticles coated with L-cysteine were used as possible contrast agents for MRI/CT imaging and were evaluated using three different glioma (brain cancer) cell lines (C6 from rat, SGH44 and U251 from humans). For the MRI measurements, the glioma cell lines were incubated with Fe–Pt-Cys nanoparticles and dissolved in medium at different iron concentrations. After 3 h the cells were washed, dispersed and suspended in agarose gel and transferred to a 96 well plate. A 3.0 T body MR scanner was then used to perform imaging. The cells were prepared in a similar manner for CT measurements except the glioma cell lines incubated with Fe–Pt-Cys nanoparticles and dissolved in medium at different platinum concentrations. IVIS Lumina XR system was used to perform CT imaging. The biocompatibility of the Fe–Pt-Cys nanoparticles was assessed using a cytotoxicity assay. Three different cell lines were used, bladder cancer (ECV304) cell line, mice fibroblast (L929) cell line and human embryonic kidney (HEK293) cell line. An MTT assay was used to determine the cytotoxicity. The results showed that the Fe–Pt-Cys nanoparticles were biocompatible as no difference in cell viability was observed. The results showed strong signals for possible use as contrast agents in MRI/CT imaging [166].

4.2.3. Fe–Pt nanoparticles in targeted drug delivery and cancer therapy

Fuchigami et al. [167] researched the effect of magnetic porous Fe–Pt nanoparticles loaded with an anticancer drug for targeted drug delivery on gastric and lung cancer cell lines. Porous Fe–Pt nanoparticles were fabricated by a hydrothermal treatment of Fe–Pt/PDDA Silica composite particles which resulted in the formation of a hollow capsule with a Fe–Pt nanoparticle shell. The hollow space was then filled with the anticancer drug doxorubicin (DOX) and coated with a lipid membrane to prevent any leaks. The cytotoxic effect of these capsules was investigated using gastric (MKN-74) and lung (RERF-A1) cancer cell lines. The cell lines were incubated under a magnetic field with Fe–Pt–Dox capsules and with just doxorubicin. The results showed that the Fe–Pt–Dox capsules were guided under magnetic field and prevented the cancer cell growth of both cell lines as well as destroying over 70% of the cancer cell lines [167].

Chen et al. [168] studied the use of photothermal therapy to target breast cancer. Fe–Pt nanoparticles were functionalised with folic acid and were used to target EMT-6 breast cancer cell line. A NIR femtosecond laser was used to activate functionalised Fe–Pt nanoparticles. Cell viability results showed that no toxicity was detected and that the nanoparticles were biocompatible. Once the Fe–Pt nanoparticles were subjected to irradiation by the laser, the photothermal effects from the nanoparticles resulted in perforation and rupture of the plasma membrane of the cancerous cells. This method has potential for targeted cancer therapy [168].

Sun et al. [169] investigated different surface coatings on Fe–Pt nanoparticles and their effect on brain tumour cells. Fe–Pt nanoparticles were coated with two different materials oleic acid/oleylamine (OA/OA) and L-cysteine (Cys). The

cytotoxicity of these coated nanoparticles was assessed on three different types of glioma cell lines (human glioma (U251), astrocytoma (U87) and neuroglioma (H4) cell lines, which are all different types of brain cancer, to determine if they can be used as a cancer therapeutic. Cell viability was determined by MTT assay. It was found that Fe–Pt–OA/OA-coated nanoparticles suppressed the growth of glioma cells when compared to Fe–Pt-Cys nanoparticles where little or no cytotoxic effect was detected. It was determined that the growth suppression of the glioma cells was due to the surface coatings. The results show that by engineering the surface coating Fe–Pt nanoparticles can be possibly used as a therapeutic cancer agent for glioma [169].

4.2.4. Fe–Pt nanoparticles for magnetic hyperthermia

Seeman et al. [170] investigated the use of tungsten oxide-coated Fe–Pt nanoparticles for possible use in magnetic hyperthermia treatment. $SiW_{11}O_{39}$-coated Fe–Pt nanoparticles were prepared and annealed at 700 °C. High-temperature annealing allowed this complex core–shell nanoparticle system to transfer into a highly ordered Fe–Pt core structure coated with an amorphous tungsten oxide layer. These nanoparticles were then characterised to examine their biocompatibility, morphological and magnetic properties. Cytotoxicity studies were carried out on rat brain astrocytes. TEM studies were used to investigate the morphology of the samples. Magnetometry and magneto-caloric measurements were carried out to determine magnetic properties and heating effect of the nanoparticles. When the tungsten atoms are neutron activated they are transformed to radioisotope W-187 which has promising potential for use in cancer therapy. High-temperature annealing resulted in an increase in the magnetic moment of Fe–Pt nanoparticles. This lead to a magnetic heating effect and a temperature increase which is important for hyperthermia. The results showed that the nanoparticles were approximately 3 nm in sizes and that non-neutron activated, amorphous tungsten oxide-coated Fe–Pt nanoparticles were biocompatible. These nanoparticles showed promise for use in radiopharmaceutical applications [170].

4.3. Metal oxide nanoparticles

4.3.1. Introduction

Titanium dioxide (TiO_2) is a widely studied material. It has been used in a variety of different areas from pigment in paints to food colourings and toothpastes to the cosmetic and pharmaceutical industry. TiO_2 has many unique features such as good biocompatibility, low toxicity, chemical stability and photocatalytic properties which makes it an attractive material for use in the biomedical industry. Due to its unique properties, lots of research has been carried out on using TiO_2 nanoparticles in different biomedical applications such as drug delivery, PDT, cell imaging, biosensors and genetic engineering [173–187]. In this review, we will discuss the use of TiO_2 nanoparticles in targeted drug delivery and PDT.

4.3.2. TiO_2 nanoparticles as nanocarriers in targeted drug delivery

Qin et al. [174] examined if loading of the nanoparticles with the drug affected its efficiency. Two methods were used to load TiO_2 nanoparticles with doxorubicin (DOX), the first non-covalent complexation (TiO_2/DOX) and the second covalent conjugation (TiO_2–DOX). These two methods were then compared by examining cytotoxicity, cellular uptake and intracellular distribution using glioma (C6) cell line from rats. TiO_2 nanoparticles coated with oleic acid were synthesised by hydrolysis to ensure high-quality and mono-crystalline nanoparticles. In order to improve the conjugation of these nanoparticles to other biomolecules, the oleic acid coating on TiO_2–OA nanoparticles was exchanged for carboxylic silane (TETT), TiO_2–TETT. DOX was covalently conjugated to TiO_2–TETT nanoparticles by the formation of amide bond between carboxyl group of TiO_2–TETT and amino group of DOX. TiO_2–DOX complexes were formed by electrostatic attraction of carboxyl group from TiO_2–TETT and amine group from DOX. The results showed that the non-covalent complexation (TiO_2/DOX) method of loading DOX exhibited greater cytotoxicity than free DOX and covalently conjugated DOX (TiO_2–DOX). Confocal laser scanning microscopy results showed that DOX from the complexation method (TiO_2/DOX) was located in the nucleus. The DOX from the conjugation method (TiO_2-DOX) was located mainly in the cytoplasm. This work shows how important the method of loading TiO_2 nanoparticles with the drug is [174]. The use of mesoporous titania nanoparticles for drug delivery was studied by Wu et al. [175]. The mesoporous titania nanoparticles were prepared via controlled hydrolysis. The cytotoxicity of these nanoparticles was investigated using human breast cancer (BT-20) cell line and MTT assay. The results showed that the nanoparticles exhibited good biocompatibility. Titania has a high affinity for phosphate species such as DNA. The titania nanoparticles were functionalised with a phosphate containing fluorescent molecule, flavin mononucleotide (FMN), for bioimaging. Intracellular imaging was carried out using the BT-20 cell line and examined using confocal laser scanning microscopy. The FMN functionalised mesoporous titania nanoparticles were then loaded with doxorubicin (DOX) and drug release and cytotoxicity studies were carried out. The results showed DOX induced cell death. The results show that mesoporous titania can be used for intracellular bioimaging and drug delivery to human breast cancer (BT-20) cells [175].

Zhang et al. [176] investigated TiO_2 nanoparticles to help develop a novel pH responsive drug delivery system for daunorubicin (DNR). DNR is an anti-cancer drug but its use is limited due to its serious side effects. The aim of this study was to develop DNR-loaded TiO_2 nanocomposites and to control the release of DNR. The cytotoxicity, drug release behaviour and cellular uptake of these DNR–TiO_2 nanocomposites were examined. The results showed that by decreasing the pH from 7.4 to 5.0 the release of DNR was accelerated. DNR–TiO_2 nanocomposites increased the cellular uptake of DNR when compared to just DNR. The cytotoxicity analysis was carried out on leukaemia (K562) cell lines and the results from MTT assay showed that the TiO_2 nanoparticles were biocompatible, DNR was

toxic but the DNR–TiO_2 nanocomposites were even more toxic. This is explained by the pH of the environment, at pH 7.4 the DNR is still conjugated to the TiO_2 nanoparticles but as the pH of the environment decreases protonation of the drug occurs. Protonation will cause the chemisorbed drug to release and the surface charge of TiO_2 to change causing the drug release process. Therefore, a high concentration of DNR is released to the cells causing them to die. By controlling the pH environment, the anticancer activity of DNR–TiO_2 nanocomposites was improved [176]. The use of TiO_2 nanoparticles as nanocarriers for drug delivery to MDR breast cancer cells was researched by Ren et al. [177]. Colloidal TiO_2 nanoparticles were synthesised by drop-wise, drop by drop, addition of titanium tetrachloride ($TiCl_4$) to cool ultrapure water, and were then separated using with ultrapure water. Doxorubicin was then added by a drop-wise method to prepare TiO_2–DOX nanocomposites. Drug release, cytotoxicity and intracellular localisation studies were carried out on both TiO_2 nanoparticles and TiO_2–DOX nanocomposites. UV–Vis, infrared spectroscopy and zeta potential measurements confirmed that DOX is absorbed onto TiO_2 nanoparticles by electrostatic interaction. It was found that the release of DOX form the TiO_2–DOX nanocomposite was pH sensitive. A pH environment of 4–5 allows DOX to be released from the surface of TiO_2 nanoparticles. The anticancer activity of TiO_2–DOX nanocomposite was investigated using the multidrug resistant MCF-7/ADM breast cancer cell line and the drug sensitive MCF-7 breast cancer cell line. The results showed that for the MCF-7 cell line the TiO_2–DOX nanocomposite showed slightly higher anticancer activity than DOX by itself. For the MDR MCF-7/ADM cell line, DOX did not show any cytotoxic effect. However, TiO_2–DOX nanocomposite was found to have a 40% cytotoxic effect. It is thought that the TiO_2–DOX nanocomposite transports the drug directly into the cells and the acidic environment triggered the release of DOX. This TiO_2–DOX nanocomposite has the potential to be used as pH controllable drug delivery system for MDR cancer therapy [177].

The possible use of TiO_2 nanoparticles as nanocarriers for targeted drug delivery was studied by Venkatasubbu et al. [178]. The TiO_2 nanoparticles were synthesised via a wet chemical method. In order to improve the biocompatibility of the TiO_2 nanoparticles surface, they were modified using polyethylene glycol (PEG) and then functionalised to folic acid ligand for active targeting of folate receptors which are abundant in cancerous cells. The drug paclitaxel (PTX) was then conjugated onto the surface of the TiO_2–PEG–FA complex. Cytotoxicity and drug release studies were carried out *in vitro*. Cytotoxicity studies were carried out on human liver cancer (HepG2) cell lines. The drug release study shows that PTX is released in an initial burst, but a sustained release happens over time. The cytotoxicity results showed that both TiO_2–PEG–FA and TiO_2–PEG–FA–PTX complexes had a toxic effect on the cells. However, the TiO_2–PEG–FA–PTX complex had a more toxic effect on the cancer cells. This work showed the potential use of TiO_2 nanoparticles as drug delivery nanocarriers [178]. Du et al. [179] investigated the use of TiO_2 nanoparticles as nanocarriers for a drug delivery system. TiO_2

nanoparticles were coated with polyethylene glycol (PEG) to improve biocompatibility and functionalisation potential. The TiO_2–PEG nanoparticles were then loaded with doxorubicin (DOX) and intracellular localisation, cell viability, drug release and cytotoxicity studies were carried out *in vitro* using the MDA-MB-231-GFP-fLuc breast cancer cell line. The drug release studies again show that it is dependent on the pH environment. It was found that over 80% of DOX was released from TiO_2–PEG–DOX nanoparticles when the pH was around 5, which is typical for tumours. Only 50% of DOX was released from TiO_2–PEG–DOX nanoparticles when the pH was 7.4. Cell viability studies showed that DOX was more cytotoxic than TiO_2–PEG–DOX nanoparticles after 24 and 48 h incubations. However, after 72 h TiO_2–PEG–DOX nanoparticles showed a more cytotoxic effect to the cells than DOX. It is thought that TiO_2–PEG–DOX nanoparticles possess a prolonged drug release mechanism and higher antitumour capabilities. *In vivo* studies were carried out on orthotopic breast tumour bearing mice. TiO_2, DOX and TiO_2–PEG–DOX nanoparticles were injected into the tails of the mice. The tumour growth and drug efficiency were monitored by bioluminescence imaging. The results showed that TiO_2–PEG–DOX nanoparticles inhibited tumour growth and no obvious side effects were observed when compared to DOX. This study concluded that PEG-coated TiO_2 nanoparticles were safe and efficient for use as nanocarriers for drug delivery [179].

4.3.3. TiO_2 Nanoparticles as photosensitiser agents for PDT

Lagopati et al. [180] studied the potential use of TiO_2 nanoparticles for photocatalytic treatment of cancer. TiO_2 aqueous dispersions were prepared via a sol–gel process. Two breast cancer epithelial cell lines (MCF-7 and MDA-MB-436) were cultured for this experiment. Different concentrations of TiO_2 nanoparticles were seeded onto the cultured cell lines and irradiated for 20 min using UV-A light at wavelength 350 nm. These cells were then further cultured for 48 h before cell viability, flow cytometry and western blot analyses were carried out. The results showed that the toxicity effect of TiO_2 nanoparticles on the cells is cell dependent as there was no effect detected on the MCF-7 cells, whereas for the same concentration, cell apoptosis was detected for MDA-MB-436 cell line. Further work is needed to optimise this photocatalytic cancer treatment as UVA irradiation can damage healthy cells [180]. The photoexcitation of TiO_2 nanoparticles was investigated to inhibit the growth of malignant glioma cells by Wang et al. [181]. *In vitro* and *in vivo* studies were carried out using U87-MG brain cancer cell line and female BALB/c-nude mice which were injected with glioma cells and the TiO_2 suspension was injected under the skin. For the *in vitro* study, the U87-MG cells were cultured and incubated with a TiO_2 nanoparticle suspension for 4, 12 and 24 h. UVA irradiation was carried out using a UV lamp with wavelength <330 nm. Microscopy and cytotoxicity studies were also carried out. TEM studies showed that TiO_2 nanoparticles were rapidly internalised and nanoparticles entered the cells by phagocytosis. Cytotoxicity studies were carried out using MTT assay to

determine cell viability. It was found that TiO_2 nanoparticles had no cytotoxic effect on the cells. Once the TiO_2 particles were irradiated with UVA light, the cell viability decreased to 40%. For *in vivo* studies, the effect of TiO_2 nanoparticles with and without UVA irradiation was analysed. The results showed that the use of TiO_2 nanoparticles and UVA induced necrosis and apoptosis. The tumour growth was also inhibited and increased the survival time of the mice. These results suggest the potential use of TiO_2 nanoparticles and UVA irradiation as a treatment for brain cancer. However, more research is needed [181].

Clinical applications of TiO_2 nanoparticles as photosensitiser agents for PDT is limited as TiO_2 nanoparticles can only be activated by ultra violet light. UV light is absorbed and scattered by tissues and can penetrate the skin depending on the wavelength used. UV light can also cause damage to cells and tissues [182]. For these reasons, researchers have been developing ways to still use TiO_2 nanoparticles as photosensitisers but activate them using different methods. Hu et al. [183] examined using visible light to induce photodynamic activities from graphene oxide/TiO_2 hybrid. Graphene oxide (GO) was prepared by Hummers method, this graphene oxide was then used in the synthesis of graphene oxide/TiO_2 (GOT) which was prepared by self-assembly method. These GOT hybrids were then characterised using various different techniques such as TEM, XPS, XRD, UV–Vis, AFM and Raman spectroscopy. Cytotoxicity and flow cytometry studies were carried out on cervical cancer (HeLa) cell line. For the cytotoxicity studies, the HeLa cells were cultured and incubated for 1 h with GOT. The cells were then exposed to visible light (>400 nm), in order to protect the cells from heat damage, a heat shield was placed in front of the visible light source. Following irradiation, the cells and GOT were further incubated for 24 h. Cell viability studies were then carried out using MTT assay. It was found that cell viability was dependent on irradiation time and ROS generation induced cell death. The results showed that GOT had good photodynamic anticancer activity [183].

Idris et al. [184] investigated photoactivation of up-conversion nanoparticles (UCN) coated with TiO_2 and their effect on normal human lung fibroblasts (HLF), IMR-90 cell line (lung) and human oral squamous cell carcinoma (OSCC), CAL-27 cell line (tongue). Based on the up-conversion process, rare earth nanomaterials have the ability to absorb NIR light and emit a higher energy light in UV/visible spectrum. Using NIR light, the damage to cells and tissues is reduced and deeper penetration into the tissue is achieved. For this experiment, the up-conversion nanoparticles are coated with TiO_2 to produce a core–shell nanocomposite. UCN acts as a transducer and TiO_2 acts as a photocatalyst. Cell imaging and cytotoxicity studies were carried out. Both cell lines were cultured and exposed to different concentrations of the TiO_2–UCN nanocomposite. After 6 h, the cells were exposed to 980 nm laser for 5 min and 20 s and incubated for a further 24 h. Cell viability tests were then carried out using CellTiter 96® AQueous One Solution Cell Proliferation Assay, which is a colorimetric method used to determine the number of viable cells. The results showed that up-conversion of NIR to UV/visible light

which induced photoactivation of TiO_2. This resulted in the generation of ROS which induced cell death. This treatment could potentially be used for treatment of deep-seated tumours [184].

Lee et al. [185] researched the use of defective TiO_2 (d-TiO_2) nanoparticles for the photocatalytic destruction of human cervical (HeLa) cancer cells and hepatocellular (liver) (Hep-G2) cancer cells using long wave-length visible light. The defective TiO_2 (d-TiO_2) nanoparticles were synthesised via sol–gel and hydrothermal reactions through the formation of liposome-TiO_2 composites. The structural, optical and cytotoxic properties of the (d-TiO_2) nanoparticles were examined. Cytotoxicity studies were carried out on HeLa and Hep-G2 cell lines. The cell lines were cultured and seeded on 96 well plates for 24 h after which varying concentrations of (d-TiO_2) nanoparticles and P25 TiO_2 were added for further 24 h incubation. These were then irradiated for 4 h with visible light from a 300 W xenon lamp. A 400 nm long pass filter and a heat absorbing coloured glass filter were used to remove the UV and far infrared wavelengths. Cell viability was measured by the WST method. Singlet oxygen generation was also monitored by a singlet oxygen sensor green reagent. The results showed the generation of ROS and also singlet oxygen, after irradiation with long-wavelength visible light, which lead to the destruction of the cancerous cells. Defective TiO_2 (d-TiO_2) nanoparticles show good potential for use in PDT for cancer treatment [185].

5. Conclusions

From this review, it can be seen that the use of iron oxide nanoparticles in biomedical applications is still a highly researched area. The aim of this review was to investigate the use of lesser studied nanoparticles such as Ag, Fe–Pt and TiO_2, for possible use in biomedical applications. Ag nanoparticles show high electrical conductivity, high thermal conductivity, chemical stability, catalytic activity and enhanced Raman scattering and these properties have been used successfully in drug delivery and cancer therapy. Fe–Pt nanoparticles exhibit unique properties such as superparamagnetism, high coercivity, chemical stability, oxidation resistance and biocompatibility making them appealing materials for use in magnetic hyperthermia, MRI contrast agents, drug delivery and biosensors. Fe–Pt nanoparticles have been shown to lower T_2 relaxation times for MRI imaging and as successful drug carriers for targeted drug delivery. More research is needed for potential use in magnetic hyperthermia. TiO_2 nanoparticles have many unique properties such as biocompatibility, chemical stability and photocatalytic properties which have led to an increase in the use of these nanoparticles in drug delivery, bio-imaging, photoablation therapy and biosensors. TiO_2 nanoparticles were shown to be successful nanocarriers for drug delivery. The photocatalytic property of TiO_2 nanoparticles has made it popular as photosensitiser agents for photodynamic therapy; however, more research is needed in this area.

Abbreviations/acronyms

AFM	Atomic Force Microscopy
AML	Acute Myeloid Leukaemia
CT	Computed Tomography
Cys	L-Cysteine
DLS	Dynamic Light Scattering
DNA	Deoxyribonucleic acid
DNR	Daunorubicin
DOX	Doxorubicin
FA	Folic Acid
FITC	Fluorescein-isothiocyanate
FMN	Flavin Mononucleotide
GO	Graphene Oxide
GOT	Graphene Oxide/TiO_2
LDH	Lactate Dehydrogenase
MDR	Multi-drug Resistant
MRI	Magnetic Resonance Imaging
M_s	Saturation Magnetisation
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NIR	Near Infrared
OA	Oleic Acid
OA/OA	Oleic Acid/Oleylamine
PBS	Phosphate Buffer Solution
PDDA	poly(diaryldimethylammonium chloride)
PEG	Polyethylene Glycol
PET	Positron Emission Tomography
PTX	Paclitaxel
PVP	Polyvinylpyrrolidone
ROS	Reactive Oxygen Species
TAT	Trans-Activating Transcriptional Activator
TEG	Tetraethylene glycol
TEM	Transmission Electron Microscopy
TETT	N-(Tri-methoxysilylpropyl) ethylene diamine triacetic acid, trisodium salt
UV	Ultraviolet
UCN	Upconversion Nanoparticles
WST	Wedge Splitting Test
XPS	X-Ray Photoelectron Spectroscopy
XRD	X-Ray Diffraction

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Appendix 1.

Cell line	Species	Cancer type
MCF-7	Human	Breast cancer
MCF-7/ADR		
MCF-7/ADM		
MDA-MB-231		
MDA-MB-436		
BT-20		
EMT-6	Mouse	
SHI-1	Human	Bone marrow/white blood cells
THP-1		
NB-4		
HL-60		
DMAI		
HEL		
K562		
C6	Rat	Brain/spine
SGH44	Human	
U251		
U87		
H4		
HEK293	Human	Kidney
Vero	Monkey	
ECV304	Human	Bladder
MBT-2	Mouse	
HT29	Human	Colon
Caco-2		
B16	Mouse	Skin
HeLa	Human	Cervical
MKN-74	Human	Stomach
RERF-A1	Human	Lung
IMR-90		
HepG2	Human	Liver
Cal-27	Human	Tongue
OECM-1	Human	Oral