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Metallic nanoparticles: technology overview & drug delivery applications in oncology

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Importance of the field: The targeted delivery of therapeutic agents to tumour cells is a challenge because most of the chemotherapeutic agents distribute to the whole body, which results in general toxicity and poor acceptance by patients and sometimes discontinuation of the treatment. Metallic nanoparticles have been used for a huge number of applications in various areas of medical treatment. Metallic nanoparticles are emerging as new carrier and contrast agents in cancer treatment. These metallic nanoparticles have been used for imaging of tumour cells by means of active and passive targeting. Recent advances have opened the way to site-specific targeting and drug delivery by these nanoparticles.

Areas covered in this review: This review summarizes the mechanisms of passive and active targeted drug delivery by metallic nanoparticles and their potential use in cancer theranostics.

What the reader will gain: The reader will gain information on the development of tumour cells, advantages of modern methods of cancer treatment over the traditional method, targeted delivery of anticancer agents using nanoparticles, influence of nanotechnology on the quality and expectancy of life, and challenges, implications and future prospects of metallic nanoparticles as probes in cancer treatment.

Take home message: The development of metallic nanoparticles is rapid and multidirectional, and the improved practical potential of metallic nanoparticle highlights their potency as new tools for future cancer therapeutics modalities.

Keywords: enhanced permeability and retention, metallic nanoparticle, multifunctional nanoparticle, nanoshell, opsonisation, theranostic, tumour cell

Expert Opin. Drug Deliv. (2010) 7(8):927-942

1. Introduction

Cancer is the second leading cause of death in both developed and developing countries [1]. At present, first-line cancer therapy involves invasive processes such as catheters to allow chemotherapy to shrink any tumour present and surgical removal of the tumour followed by a regimen of chemotherapy and/or radiation therapy. The main goal of chemotherapy and radiation therapy is to kill the cancer cells. In this, the effectiveness of the therapy is directly related to the treatment's ability to target and kill the tumour cells while affecting as few healthy cells as possible. This in

10.1517/17425247.2010.498473 © 2010 Informa UK Ltd ISSN 1742-5247

Article highlights.

- Modern treatment of cancer has become more tailored to the individual patient and to specific tumour types.
- Metallic nanoparticle probes are emerging as a class of new contrast and tracking agents for tumour imaging.
- Enabled by their super molecular structures, metallic nanoparticle are capable agents in the detection, diagnosis and treatment of tumour.
- Multifunctional metallic nanoparticles can detect the early onset of cancer in each individual and deliver suitable therapeutic agent.
- Traditionally, the treatment and diagnosis of tumour were considered as two separate entities in the process of patient care; the emergence of the theranostic nanoconcept has blurred the boundary between treatment and diagnosis.
- As the capability of multifunctional metallic nanoparticles continues to increase, the integration of oncology research, diagnostic imaging and targeted drug delivery will be essential for cancer therapy.

This box summarizes key points contained in the article.

turn is related to the quality of life and life expectancy of patients. Unfortunately, this strategy often fails because of recurrent or metastatic disease. In some cases, the patients must discontinue the chemotherapy before the drug has a chance to eradicate the tumour because of its intense side effects [2,3].

The use of various pharmaceutical carriers to enhance the *in vivo* efficiency of anticancer drug(s) and drug delivery protocols has been well established during the last four decades of oncology research. One of the most important results of this research is the 'development of metallic nanoparticles to fight cancer'. These metallic nanoparticles may be the key to overcoming some of the limitation of conventional diagnostic and therapeutic approaches. The use of metallic nanoparticles for targeting cancer has significant advantages, such as increased stability and half-life of drug carrier in circulation, required biodistribution, and passive or active targeting into the required tumour site.

1.1 Development of tumour cells

Cancer is a general term used for a group of disorders caused by an abnormal and unrestricted growth of cells. Once a small mass of tumour is formed, it will compete with the surrounding healthy tissue for nutrients from the blood. As the healthy tissues are not able to compete with cancer cells for an adequate supply of nutrients, the tumour cells replicate at a rate higher than the other surrounding healthy cells and place a strain on the supply of nutrients and elimination of metabolic wastes [4-7]. As a tumour grows, its need for nutrients increases, and thus the number and size of blood vessels needed to transport them increase proportionately. To facilitate this process the tumour produces vascular growth factors that promote angiogenesis (neovascularisation) and/or other factors that normally promote angiogenesis. The exact mechanisms that initiate angiogenesis at a tumour site are not yet known. Further, angiogenesis is aided by the secretion of proteolytic enzymes, namely metalloproteinase, which facilitate the passage of tumour through the basement membranes and into the extracellular matrix of the local connective tissue. An illustration of tumour development from a single cell is shown in **Figure 1**.

2. Metallic nanoparticles for cancer theranostic

Many new drugs are being synthesised for the treatment of cancer; however, the clinical potential of such drugs is subjected to certain therapeutic and toxicological limitations, such as the barrier effect of the cell membrane, drug resistance developed by the cell and drug disposition behaviour [8]. In a cancer cell, the transportation of a drug is also governed by the physicochemical properties of the interstitium and molecule (i.e., size, configuration, charge and hydrophobicity) [9]. The distribution of anticancer drugs essentially depends on their physiochemical properties, such as p*K*a, hydrophilicity and electrostatic charges; however, not all of these criteria necessarily fit in the domain of a tumour cell. Large amounts of the drug can be distributed towards a healthy organ or tissue rather than the target, and this is the main limiting factor of conventional chemotherapy [10]. In addition, at the cellular level drug resistance may develop in a tumour cell on account of alterations in the P-Glycoprotein system or distorted apoptosis regulation [11].

Another dilemma associated with chemotherapy is the inherent insolubility of most of the anticancer drugs in water, which necessitates the use of pharmaceutical solvents for their clinical administration. The use of these solvents may have life-threatening effects [2,12].

In conventional therapy, during intravenous injection of an anticancer drug, the drug delivery system is opsonised and rapidly cleared from the bloodstream by the reticuloendothelial system's defence mechanism, irrespective of particle composition [12-16]. Consequently, conventional anticancer therapy by systemic delivery of chemotherapeutic agents often fails or is inadequately delivered to the target cell/tissue and has a tremendous impact on reducing the quality and expectancy of life. Some of the disadvantages of current conventional anticancer therapy include: inefficient cell entry, uptake by the immune system and mononuclear phagocyte system, accumulation in non-targeted organs and tissues, and non-selective with high toxicity against normal tissues [17]. The effectiveness of a cancer therapeutic device is measured by its ability to reduce and eliminate tumours without damaging healthy tissue.

The ultimate goal of anticancer therapy should be to prolong the survival time and increase the quality of life of the patient. Therefore, the greatest need for the treatment of tumour is a drug delivery system that can selectively deliver

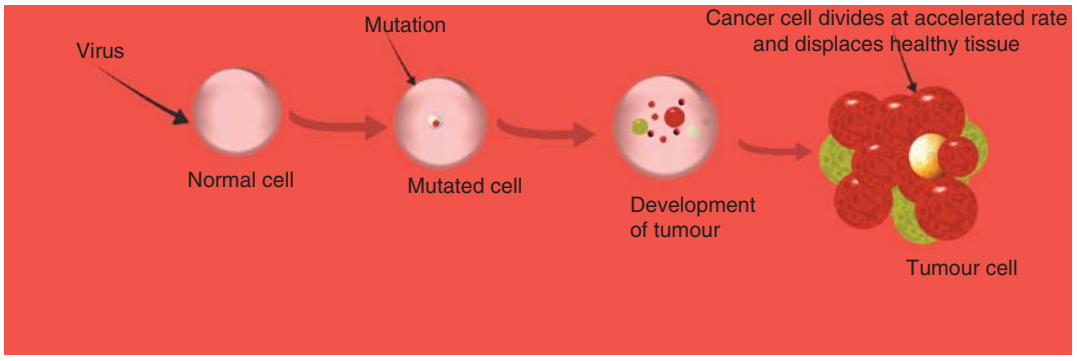

Figure 1. Tumour development from a single cell.

anticancer agents to the target tissue with required local drug concentrations, thereby achieving therapeutic efficacy while minimising toxic side effects. To achieve this, a multifunctional therapeutic agent capable of destroying the heterogeneous population of tumour cells needs to be developed. Recently, drug delivery systems such as nanometre-sized carriers that entrap the chemotherapeutic drugs have improved cancer treatment [18-23].

Metallic nanoparticles for drug delivery are solid colloidal particles ranging in size from 10 to 1000 nm that contain a therapeutic agent that is dispersed in a polymer carrier matrix, encapsulated within a polymer shell, covalently attached or adsorbed to the particle surface, or encapsulated within a structure [24-26].

Metallic nanoparticle seeks to increase the therapeutic index of drugs through site specificity, preventing multidrug resistance, and delivering therapeutic agents efficiently [3,27]. Several nanoparticle-based systems are now being explored for cancer treatment. The material properties of each nanoparticle system have been developed to enhance delivery to tumours [28-35]. Among these, metallic nanoparticle probes are emerging as a new class of contrast and tracking agent for cancer therapies [36-45].

Metallic nanoparticles are emerging as a potential application in the field of cancer diagnosis, for example MRI and colloidal mediators for cancer magnetic hyperthermia. The usefulness of metallic nanoparticles as probes for cancer therapy is mainly derived from their potential to carry a large dose of drug, which results in high concentration of anticancer drugs at the desired site, thus avoiding toxicity and other painstaking side effects arising owing to high drug concentration in other parts of the body [39].

There are many advantages of metallic nanoparticle in cancer therapeutics. For example, they are designed to contain tumour targeting ligands that bind to particular cells within the tumour to fasten the nanoparticle within solid tumour. In this way, metallic nanoparticle drug delivery systems are capable of sequestering anticancer drugs exclusively within the tumour and thereby reduce the accumulation of drugs in healthy organs. Their large surface area-to-volume ratio provides a surface for chemical modification, which can improve cell entry, protect the therapeutic agent in the biological milieu, and improve bioavailability of the anticancer agent [13-17,46,47]. Furthermore, multifunctional metallic nanoparticles can detect and attack the heterogeneous crowd of tumours (**Figure 2**).

Thus, because of their unique physical properties and capability to function at the cellular and molecular level, metallic nanoparticles are being actively investigated as carriers for targeted drug delivery in cancer therapeutics [48,49]. One of the key reasons that these nanoparticles have promise in the treatment of cancer is that they can be targeted to tumours through antigen-dependent (specific) or antigen-independent (nonspecific) mechanisms [50,51]. Specific targeting relies on the interaction of antigens on the surface of nanoparticles with tumour cell receptors [52]. Metallic nanoparticles are used to manipulate not only the size of drug particles but also the physical characteristics, and thus the extent and target of drug delivery. In brief, the use of metallic nanoparticles for cancer treatment has significant advantages, for example, the ability of metallic nanoparticles to target specific tumour cells, accumulation of therapeutic agent in the vicinity of tumour, and reduction of drug concentration in healthy cells/tissue.

This sophisticated technique in cancer therapeutics is progressing very quickly, in terms of both newly discovered anticancer agent, and advanced ways of delivering both new and old anticancer agents. The functionality of fabricated metallic nanoparticle may be exploited to enhance the specificity of drug delivery towards tumour cells and reduce toxicity. Using metallic nanoparticles, cancer therapy could be performed at the cellular and subcellular levels, therefore side effects could be reduced and therapeutic efficacy greatly increased. Thus, application of metallic nanoparticles in cancer therapeutics is potentially the largest public health contribution of nanoscience. In this review, the following are covered: targeting the tumour cells using metallic nanoparticles, developments and theranostic applications of metallic nanoparticles in

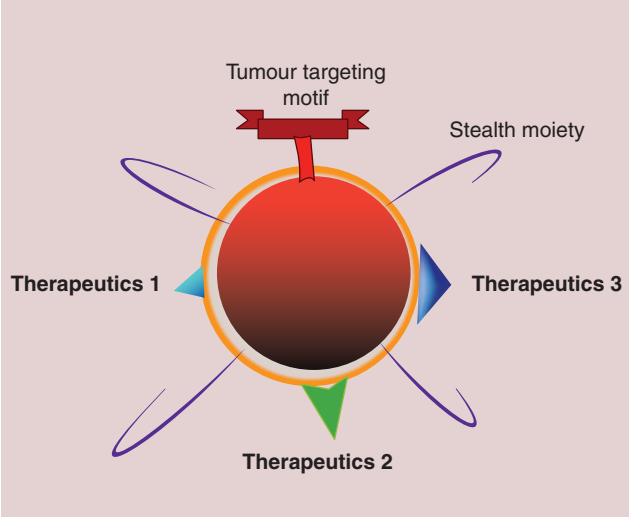

Figure 2. Multifunctional metallic nanoparticle.

oncology disorders, and an overview of risk assessment in the area of metallic nanoparticles in cancer therapeutics.

3. Targeted delivery and biological consideration

Conventionally, anticancer drugs have been designed to have a relatively low molecular mass and an agreement between the hydrophilic and lyphophilic balance (HLB), hence allowing partitioning across the lipid membrane very easily. Therefore, drug within the systemic circulation is rapidly distributed throughout the body, reaching the target and non-target tissue/organ, and is also rapidly metabolised by the liver and/or rapidly excreted by the kidney. Therefore, for effective targeting, it is essential that a drug-targeting system should not be cleared out quickly from the body. Ideally, a drug carrier should provide a pharmacokinetic profile that will allow the drug to interact with its target [17,53]. During the designing of metallic nanoparticles, the lessons learned from the polymer-based and liposomal drug delivery system must be taken into consideration. For example, unprotected liposomal and polymer-based drug delivery systems are rapidly cleared from the blood by the reticuloendothelial system (RES) and accumulate in the liver, conditioning their rapid first-pass metabolism from the systemic circulation followed by metabolic degradation and excretion. This consideration is very beneficial when designing metallic nanoparticles for cancer therapeutics located close to the mononuclear phagocyte system [21,53-58].

The performance of nanoparticles inside the vascular compartment is controlled by complex factors such as their shape, density, size distribution and surface characteristics. All these factors control the flow properties of nanoparticles, bifurcation in the vascular compartment, modulation of circulation time, and mode of entry into the cell [22,59-64].

3.1 Achieving targeted delivery

A major barrier that a drug delivery system must be able to avoid in the systemic circulation is the removal of nanoparticles by phagocytic cells of the mononuclear phagocyte system (MPS). Nanoparticles will usually be taken up by the liver, spleen and other parts of the RES depending on their surface characteristics and undergo opsonisation in the blood and clearance by the RES [16,65-69]. Therefore, the MPS presents a significant barrier to effective drug targeting, because it has the ability to filter out and destroy a drug delivery system unless appropriate formulation approaches are used to avoid this. Therefore, the nanoparticles should be designed to avoid these interactions, particularly opsonisation, and possible clearance of the drug delivery system from the vascular compartment. Opsonisation is a process in which the surface of the foreign particles such as bacteria and particulate drug carrier is coated with blood proteins, known as opsonins. The phagocytosis of these tagged particles is enhanced because surface receptors present on phagocytes bind to opsonins and the foreign particle is engulfed and untimely digested by various lysozymes [58,69-72]. For example, when unprotected colloidal nanoparticles were intravenously injected into mouse, it was observed that 95% of the gold nanoparticles were cleared out from the vascular compartment within 10 min [45]. Therefore, suppression of opsonisation and avoiding MPS recognition and receptor-mediated phagocytosis are the primary concerns when designing metallic nanoparticles.

A more practical approach to avoid RES uptake and clearance of nanoparticles is the modification of nanoparticles' surface. For example, increasing the surface hydrophilicity, that is, adding a hydrophilic polymer to the metallic nanoparticle carriers, made them invisible to the RES and thus reduced opsonisation and led to suppression of macrophage recognition. This coating is referred to as the stealth moiety (e.g., **Figure 2**) [73,74]. The most commonly used stealth agent is polyethylene glycol (PEG) and its block copolymer. It has been proposed that PEG has a high local concentration of hydrated groups, which sterically inhibits interaction with blood-borne opsonins [50]. Intravenous injections of sterically stabilised nanoparticles result in prolonged circulation time, and their accumulation in tumour [75-82].

Another factor affecting the opsonins' binding are physicochemical properties of the nanoparticles (i.e., surface characteristics such as size, surface charge) [58,83-92], which is a major factor in the characteristic biodistribution and residence times of these particles *in vivo*. Neutral systems tend to remain longer in blood circulation, whereas their charged counterparts are cleared out by the RES [3,58]. Similarly, particles of size ~ 1 – 2 μm undergo phagocytosis, and higher sizes of ~ 6 μm are trapped in lung capillaries [53]. Therefore, to avoid clearance by the RES, metallic nanoparticles should be formulated to be not more than 100 nm in size and should have a sterically stabilised, preferably neutral, surface.

3.2 Passive targeting of tumours using metallic nanoparticles

In passive targeting, the distribution of nanoparticles is mediated by the MPS's physiological condition. In passive targeting, advantage is taken of the pathological condition of the tumour to allow the accumulation of drug carriers at the target site [90]. For example, the pH or specific enzymes present within the tumour cells can be used to facilitate the release of drugs from nanoparticles. Enzymes such as alkaline phosphatase and plasmins are present at a higher level at the tumour site.

Once a tumour mass has formed, normal cells are ultimately displaced. Also, solid tumour secretes factors that cause new blood vessels to grow from existing blood vessels towards the tumour, and this growth process, known as angiogenesis, is initiated when the volume of the tumour becomes 2 mm^3 [91]. Tumour vasculature originating from the host vasculature is significantly different and is abnormal in the diseased tissue. In tumour cells, one of the characteristic features of angiogenesis is that it has aberrant tortuousity and abnormalities in the basement membrane [92]. This incomplete vasculature of tumour results in leaky blood vessels (capillaries). This hyperpermeability of the tumour vasculature is a key feature in passive targeting of drug carriers [93-96]. The disorganised pathology of angiogenic tumour vasculature with its discontinuous endothelium leads to hyperpermeability to circulating nanocarrier, and a lack of effective tumour lymphatic drainage, which leads to subsequent accumulation of drug carrier. This is called the enhanced permeability and retention (EPR) effect (**Figure 3**) [81,97,98]. The EPR effect has been observed in many animal models and also in human solid tumour. A high level of permeability factor such as nitric oxide and vascular endothelial growth factors enhance the permeability of blood vessels, thus supporting EPR [64].

Although the EPR effect is very effective for intravenous delivery of nanovector, a major obstacle associated with EPR is accumulation of drug-loaded nanovector within blood capillaries away from the tumour cell [45]. This is mainly owing to the formation of an intratumour clot, which results in increased interstitial fluid pressure (IFP) of solid tumour. As a result of the higher interstitial pressure, poor lymphatic drainage and continued angiogenesis, movement of particulate materials out of the tumour blood vessels and into the extravascular compartment is remarkably limited [45,60]. Electron microscopic visualisation of blood vessels in solid tumour showed that thickness of the blood vessel wall is poorly correlated to its diameter; therefore, in a tumour blood flow is chaotic [99,100]. Surface charge and hydrophobicity of metallic nanoparticles can affect their biodistribution by interaction of metallic nanoparticles with plasma protein, adaptive immune system and extracellular matrices [101,102].

3.3 Active targeting of tumour using metallic nanoparticles

As passive targeting does not necessarily guarantee the internalisation of nanoparticles by the targeted cell, nanoparticles are modified with molecular targeting ligands for active targeting of tumour. It is a well-known fact that cancer cells express specific surface receptors that can be targeted [103], for example, some tumour cells express surface enzymes that might be useful to activate a prodrug once a nanoparticle has been localised on the surface of the tumour [104].

Active targeting of metallic nanoparticles involves an interaction between peripherally conjugated targeting moiety and a corresponding receptor to facilitate the targeting of a carrier to a specific malignant cell [105-107]. Drug delivery to the tumour cell can be achieved by means of molecules that are specific to antigens or receptors expressed on the surface of a tumour cell [18,108]). Ligand can be designed to have specificity for receptors that are expressed on a tumour cell but are minimally expressed on normal cells. The introduction of targeting ligand enhances the internalisation of metallic nanoparticles into the tumour cell. However, care must be taken when selecting ligands for receptors on the tumour cell, as ligand–receptor interaction can affect the rate of internalisation, which in turn affects the accumulation of metallic nanoparticles in cancer cells. Therefore, ligands used for receptor targeting in cancer treatment must have the function of inducing receptor-mediated endocytosis (RME) [109].

These ligands (antibodies, saccharides, aptamers, hormones, lectin and low-molecular-mass compounds) bind to their specific receptor on the cellular surface and trigger the internalisation process of drug delivery so that anticancer drugs act on intracellular targets (e.g., mitchondria, microtubules, nucleus, etc.) by means of RME (**Figure 4**) [18,110]. Various molecules are used to facilitate active targeting of nanoparticles, such as aptamers [111-113], proteins and antibodies (**Figure 4**) [113-115]. Bioconjugation of ligands, such as monoclonal antibodies, proteins, or peptides, with the nanocarrier's surface has been exploited in many nanoparticles for the purpose of concentrating therapeutic action on the specific tumour cell [3,18,45,52,116-122].

Several overexpressed growth factor receptors have been used for selectively targeting the cancer cell, and the description of many of these targets has been reviewed [123].

3.3.1 Targeting with HER2/neu

Monoclonal antibodies were the first targeting agents to deliver the magnetic nanoparticle [124,125]. Herceptin, an FDA-approved monoclonal antibody, is a popular targeting agent for the HER2/neu receptor for breast and ovarian cancer [126]. Huh *et al.* reported the specific delivery of Herceptin-targeted magnetic nanoparticles to the cells expressing the HER2/neu cancer marker *in vivo* [127]. Unfortunately, this antibody can also target normal cardiac cells undergoing repair induced by the actions of a common anticancer agent, doxorubicin. Therefore, nanoparticles having a cytotoxic capacity and targeted using the herceptin antibody could result in cardiomyopathy [128].

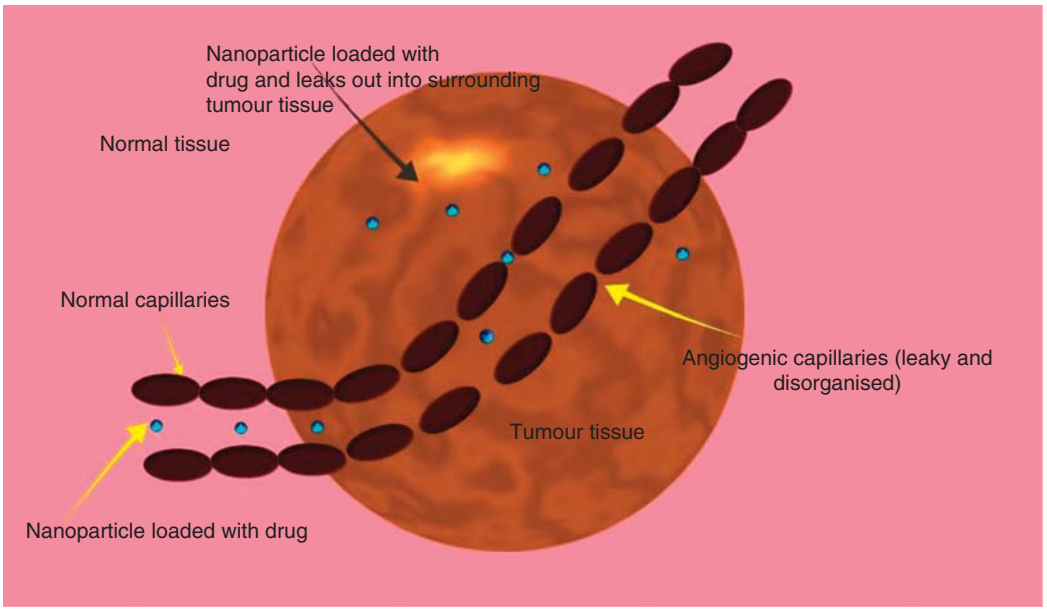

Figure 3. Enhanced permeability and retention leads to increased permeability of the capillary at sites of tumour, which can facilitate the escape of nanoparticles loaded with drug from the circulation.

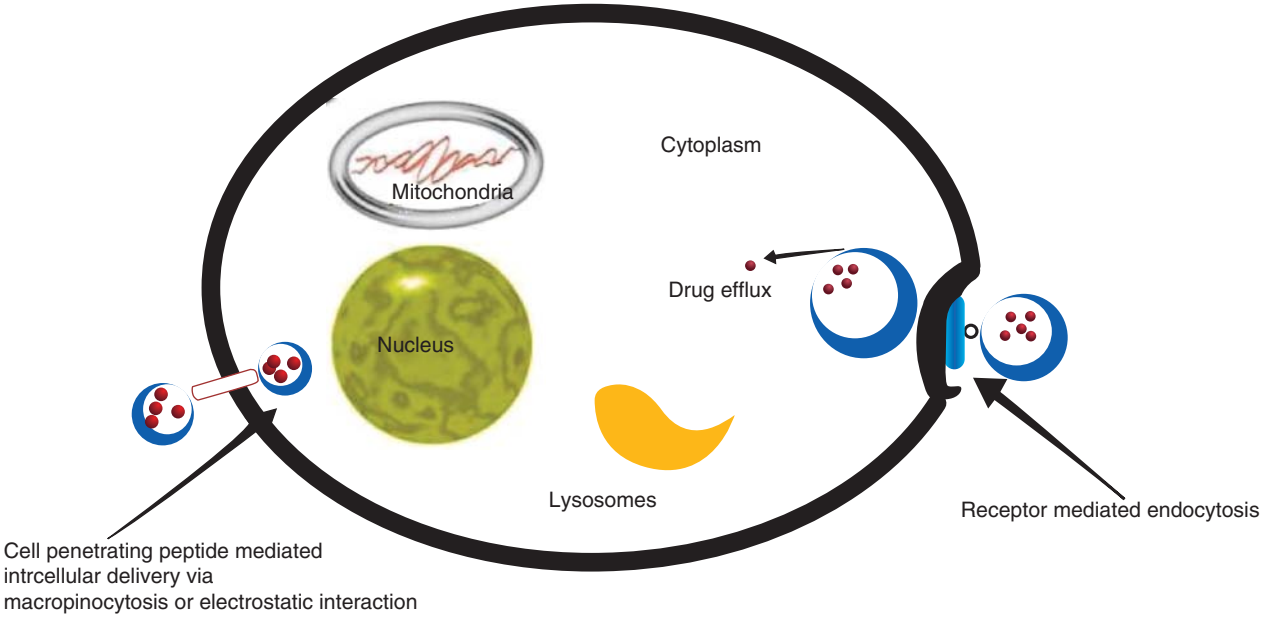

Figure 4. Schematic of intracellular drug delivery.

3.3.2 *Folate receptor*

Folate receptor is weakly expressed in normal tissue but is overexpressed on the surface of tumour cells, thus making it possible to target several tumour cells. Folic acid and its reduced form tetrahydrofolate are cofactors of several enzymes. Folic acid and tetrahydrofolate are used as targeting molecules because of its low molecular mass and low immunogenicity [129]. Thus, targeting the folic acid receptors is interesting for drug delivery in cancer treatment.

3.3.3 *Targeting multivalent carriers*

Specificity of nanoparticles can be improved significantly by the attachment of multivalent targeting ligands. These multifunctional nanoparticles can combine several functional

capabilities in a single stable unit and can be used to increase the accumulation of nanoparticles within tumour cells [130].

Several studies with enhanced binding affinity have been reported where multivalent targeting ligands simultaneously bind with multiple receptors between two surfaces (**Figure 5**) [131-134]. Jiang *et al.* reported that magnetic nanoparticles of size range 25 – 50 nm are most suitable for multivalent targeting ligands; however, it was also observed that nanoparticles < 25 nm lack the ability to present multiple ligands to specific target cells [134].

4. Recent developments and applications of metallic nanoparticles in cancer theranostics

There is a long history of the use metallic nanoparticles in biological systems for diagnostic and therapeutic purposes [44]. However, the use of metallic nanoparticles in cancer therapeutics has been reported only recently. As metallic nanoparticles have the ability to treat as well as to diagnose the disease, the ability of nanoparticles both to diagnose and to deliver the targeted drug is an emerging concept in the nanoplatform. These nanoparticles are called theranostic (therapeutic plus diagnostic) [135].

Theranostic nanovector represents an emerging class of imaging and therapeutic that may provide a personalised therapeutic response. For example, light-activated theranostic nanoparticles have been reported for imaging and treatment of brain tumours [37]. Therapeutic efficacy of these agents was evaluated in comparison with untargeted particles in a diseased animal model. In this study it was reported that survival time for untargeted particle groups was 13 days, whereas animals treated with targeted agents had a survival of 33 days, with 2 animals disease-free within 180 days of therapy. The roles of theranostic agent in tumour diagnosis, monitoring tumour progression and assessment of therapeutic effect have resulted in an enhanced role. For example, *ex vivo* imaging of oncology biomarkers in a preclinical study was reported by Makino *et al.* for the visualisation and monitoring of tumour progression by coupling the near-infrared fluorescence (NIRF) and nanoparticles in a targeted drug delivery system for hepatic tumour [136]. This particle works on the fact that the wavelength (λ) of NIRF is able to penetrate deeper into tissue. In another approach, 100% cell death was observed when human transformed human macrophage was incubated with nanocarrier for 60 min and laser illumination [135]. Similarly, in another experiment Alexa 750 NIRF dye coupled with phospholipid micelle enabled the rapid imaging of tumour in mouse model for breast cancer [137]. Theranostic photosensitiser ADM06 was evaluated in rats bearing breast cancer; in this study, suppression of tumour activity was observed after 48 h [138].

Combining diagnostic and therapeutic processes into one (theranostics) and improving their selectivity to the molecular/cellular level may offer significant benefits in oncology research. Lukianova-Hleb *et al.* developed plasmonic nanobubbles (PNB) based on the nanoparticle-generated transient photothermal vapour nanobubbles. They evaluated the PNB in living lung carcinoma cell. After delivery and accumulation it was observed that PNB are capable of fast and selective damage of specific cells and guidance of the damage through the damage-specific signals of the PNB. Thus, PNB acted as theranostic agents and supported diagnosis and therapy [139]. Biodistribution of gold nanoparticles coated with gadolinium chelate was studied by Alric *et al.,* they reported that functionalised gold nanoparticle freely circulate in the blood vessels without undesirable accumulation in any major organ [140]. In another investigation Lindsey *et al.* evaluated the controlled release of liposomes containing a molecular load and gold nanoparticles. They demonstrated an optically guided release through disruption of the liposome membrane and ejection of the liposome contents with plasmonic nanobubbles [141].

Iron nanoparticles have been used as theranostic agents with specific application as contrasting agents for MRI and magnetically targeted drug deliver to the tumour cell [142-147]. There are mainly two types of iron oxide nanoparticle reported for use as imaging agents [142,148], superparamagnetic iron oxide (SPIO) and ultra-small superparamagnetic iron oxide (USPIO). The main advantages associated with SPIO nanoparticles are the biocompatible and biodegradable properties of iron, as it can be recycled through the normal biochemical pathway for iron metabolism [149]. Hepatic imaging was the first application of these magnetic nanoparticles. It was possible because normal liver cells take up SPIOs, which results in darkening of the image; however, cancerous cells are not able to take up the SPIOs, thus resulting in a bright spot in tumour cells [150-153].

There are many reports in which SPIOs have been used in combination with monoclonal antibodies to detect a variety of cancers [154-157]. Transferrin and pancreatic receptors are overexpressed in some tumours [158,159]. SPIOs have been conjugated with peptides to target these receptors and image the cancer cells. Zhao *et al*. reported that when SPIOs were linked with the peptide synaptotagmin, it enabled the imaging of cells undergoing apoptosis after chemotherapy. The magnetic nanoparticles that have been approved by the FDA are listed in **Table 1** [160-163].

Christopher *et al.* reported the synthesis and use of magnetic nanoparticle hydrogel (MagNaGel™; Alnis Biosciences, Emeryville, California, USA) as a powerful cancer treatment regimen. They demonstrated that these particles had the characteristics of ability to load chemotherapeutic agent, tumour-associated biomolecular binding and good magnetic susceptibility [141]. In another study, it was reported that dextran-coated magnetic nanoparticles showed an increased accuracy of cancer nodal staging [164,165]. These modified magnetic nanoparticles have been used for delineation of the tumour [166].

Several anticancer drugs such as doxorubicin, methotrexate and paclitaxel have been formulated with metallic nanoparticles [167-170]. Similarly, Liang *et al.* demonstrated the ability of radionuclides containing SPIOs to induce

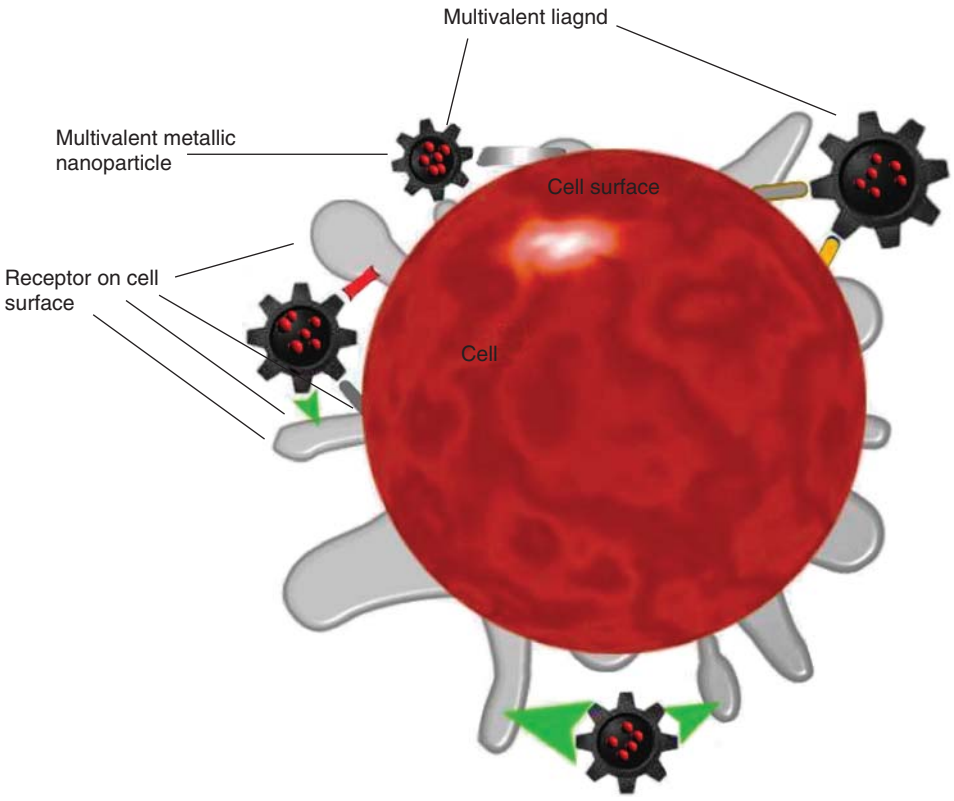

Figure 5. Conceptual illustration of multivalent affinity interaction between receptor on a cell surface and targeting ligands on a metallic nanoparticle.

Table 1. FDA-approved SPIOs.

SPIOs agents	Target organs
AMI-121	Gastrointestinal lumen
AMI-277	Blood node, lymph node
AMI-25	Liver/spleen
SHU 555A	Spleen/liver

specifically cell death in liver cells *in vitro* [171]. In another investigation, Ross *et al.* successfully demonstrated the therapeutic application of SPIOs when they were decorated with the antibody Herceptin to target the Her2/neu receptor in the early stage of breast cancer [172].

Semiconductor nanoparticles, known as quantum dots, have been increasingly applied as imaging and labelling probes in cancer therapeutics [173-177]. Major advantages associated with quantum dots include their high quantum yield, resistance to chemical modification and intrinsic fluorescence emission spectra owing to which quantum particles possess the ability to sense and release anticancer drugs at the desired site (**Figure 6**) [59].

Chen *et al.* developed a dual-function NIRF probe to assess the tumour targeting efficacy of quantum dots. They concluded that the successful development of a quantum dot-based nanoparticle with dual function may increase the accuracy of quantitative targeted NIRF imaging in tumour cells [178].

Similarly, metallic gold nanoparticles have been studied extensively for their potential application in targeted tumour cell drug delivery [177,179-184]. Gold nanoparticles have several attractive advantages in diagnostic and therapeutic applications, namely, easy decoration of gold nanoparticles with antibody for tumour-specific targeting, biocompatibility and stability [173,185].

The synergistic effect of hyperthermia and radiation therapy was studied by James *et al.* on a mouse head and neck squamous cell carcinoma model to identify the various factors affecting the efficacy of nanogold radiation therapy. They observed that radiation energy and hyperthermia influence the potential utility of gold nanoparticle for cancer radiation therapy [186]. Hybrid nanoparticles (HNP) of gold and iron oxide were synthesised and evaluated by Kirui *et al.* After biofunctionalisation of HNP with antibody that binds to A33 antigen on cancer cells, it was observed that cellular uptake of HNP was five times higher in A33-expressing cells than in normal cells. Thus, this new class of HNP can potentially act as an effective receptor-targeted therapeutic agent for tumour

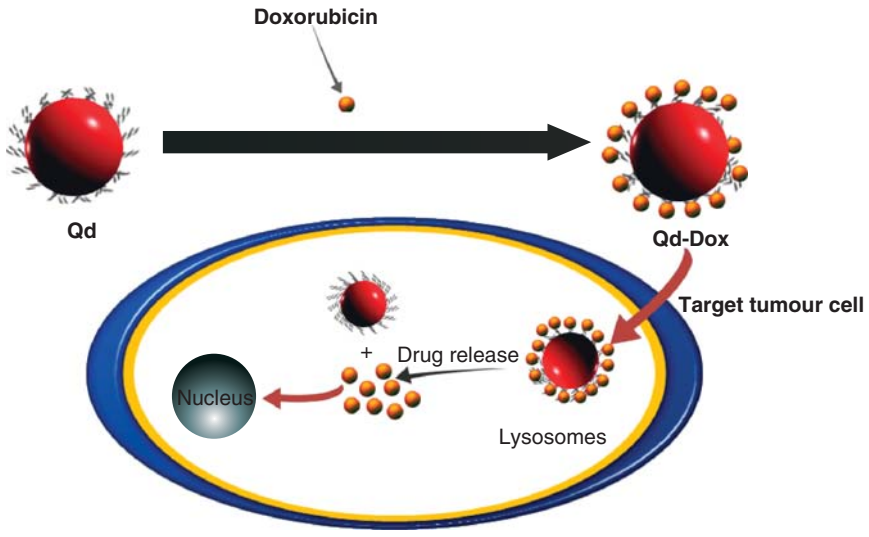

Figure 6. Illustration of Qd–Dox conjugate in targeted tumour imaging, sensing and therapy.
Dox: Doxorubicin; Qd: Quantum dots.

treatment [187]. Park *et al.* proposed a fusion system composed of metal multilayer-biodegradable polymer half-shell nanoparticles, that is, poly(lactide-*co*-glycolic acid) (PLGA)–magnetic (Mn/Au) half-shell nanoparticles loaded with rhodamine as a model drug for MRI imaging, photothermal therapy and drug delivery [188].

The first application of gold nanoshell was reported by Hirsch and co-workers in 2003 in hyperthermal therapy of tumour cells [189]. In 2005, Loo *et al.* reported the conjugation of gold nanoshell with hER2 antibody to target breast carcinoma cells [190]. When the shape of gold nanoparticles changes from nanoparticle to nananorod, their absorption and scattering wavelengths also change from visible to near-infrared region [173], owing to which gold nanorods can be used as contrast agents for dual molecular imaging. In a follow-up work by Hainfeld *et al.,* the combination of gold nanoparticles followed by X-ray treatment reduced the size of tumours in mice [191]. In one investigation, Haung *et al.* reported that cellular uptake of gold nanorods was increased twofold in malignant cells when gold nanoparticles were conjugated with antibody to target antiepidermal growth factor receptor [192]. This therapy plus diagnostic holds the promise in future of monitoring the effectiveness of therapy, and thus tailoring anticancer therapy to the individual needs of patients. However, after successful production there will be regulatory issues of nanoparticles for molecular imaging in a clinical setting. As evidence, The FDA has established a nanoparticle taskforce to handle the regulatory hurdles associated with nanomedicine [193,194].

5. Future prospects

Over the last few years, the use of metallic nanoparticles in cancer theranostic has become relatively commonplace. Research activities aimed at achieving specific and targeted delivery of anticancer agents have expanded tremendously in the last 10 years. As the capabilities of multifunctional nanoparticles continue to increase, the integration of cancer research, imaging, diagnosis and therapeutics in the future will be essential for antitumour therapy.

Much less research has been performed, however, on magnetic nanoparticles for intracellular molecular imaging. Although significant effort has been devoted to developing a metallic nanoparticle drug delivery system, metallic nanoplatforms are still at an early stage of development and much more research is required to overcome the problems associated with the nanoparticle properties influencing *in vitro* and *in vivo* toxicity assays.

6. Conclusions

The development of metallic nanoparticles is rapid and multidirectional. Metallic nanotechnology has clearly impacted the development of new theranostics in oncology disorders. Recent advances in the field of metallic nanoparticles indeed offer the promise of better diagnostic and therapeutic options. Metallic nanoparticles are attracting attention in cancer therapeutics owing to their unique prospects for targeted delivery in imaging and drug delivery to the desired site. Drug delivery based on metallic nanotechnology seeks to increase the therapeutic index of drugs, both by reaching their *in vivo* target and by exposing the drugs to malignant cells. Metallic nanotechnology combines nanobiotechnology with molecular imaging techniques, which has led to the development of multifunctional metallic nanoparticles for cancer imaging and therapy. Metallic nanoparticles have the advantage of being able to target multiple tumour markers and deliver multiple agents

in addressing the challenge of cancer heterogeneity and adaptive response. It is hoped that the new generation of multifunctional metallic nanoparticle will eventually make it possible to investigate tumours and allow the collection of vast amounts of data important for patient care. These multifunctional metallic nanoparticles offer a new era in the application of antitumour drugs in the near future. As summarised, this metallic nanoplatform plays an important role in the field of cancer therapy, and it can be expected that this nanotechnology will continue to grow over many decades.

7. Expert opinion

Cancer is a heterogeneous population of diverse diseases. Adaptive resistance of malignant cells to drugs is a major challenge to therapy. The ultimate cure for cancer is excision of the solid tumour, namely, surgical removal of cancer cells, but as discussed earlier, surgery has its own limitations, for example, the inability to distinguish between cancerous cells and normal cells in certain cases. Traditionally, diagnosis and treatment were considered as two separate entities in the process of cancer therapy; however, the merging of biology, chemistry and physics at the nanoscale has led to the emergence of nanotechnology, and in this metallic nanoparticles have blurred the boundary between diagnosis and treatment, so that these two (diagnosis and treatment) separate clinical aspects will soon merge into a single process, for example, theranostics.

Advanced developments in the nanotechnology-based drug delivery and imaging technique allow more specific mapping of tumour cells. The larger surface area-to-volume ratio of nanoparticles enables them to accommodate different functional groups on their surface. As a result of the EPR effect, metallic nanoparticles display the ability to concentrate preferentially at the cancer tissue. Metallic nanoparticles have a large impact on cancer treatment. Early diagnosis and targeted drug delivery in cancer therapeutics is one of the priority research areas in which metallic nanoparticles will play a vital role. Metallic nanoparticles have been gradually developed as a new modality for targeted drug delivery and diagnosis in cancer therapeutics. Tumour treatment has become more tailored to individual requirement and to a particular cancer cell/tissue. The integration of theranostic nanovector with diagnostic and imaging capability with therapy is critical for addressing the challenge of multi-drug resistance in cancer diversity and adaption. As the capability of multifunctional theranostics continues to increase, the integration of cancer research, imaging, diagnosis and therapeutics in the future will be essential for cancer therapy. With the advances in integration of oncology research, diagnostic imaging, therapeutics and explosive developments in nanocomposite materials science, there is reason to be optimistic that we are near a major breakthrough in antitumour therapy.

Despite all these advantages, metallic nanoparticles are still at an early stage of development. Some great achievements have been attained in this field, but many challenges remain. Most of the current theranostic nanoparticle systems have been developed for a limited number of approved drugs. For many new anticancer drugs with diverse physicochemical properties, theranostic agents need to be tailored to increase their compatibility with these drugs to achieve precise diagnosis, imaging and therapeutic payload.

A problem that may limit the wide use of theranostic nanotechnology is the toxicity of nanoparticles. The development of theranostic nanoparticles requires significant advances in nanocomposite materials science. Use of theranostic nanoparticles in the clinical setting has yet to come to fruition; therefore, the development of this agent for clinical application must be viewed as a long-term matter. However, its development is rapid and multidirectional, and the improved practical potential of metallic nanoparticles highlights their potency as new tools for future cancer therapeutic modalities. Most importantly, metallic nanotechnology must follow precise safety study.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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