4 Theranostics Nanoformulations: Merging Diagnostics and Nanotherapeutics

Shubham Khot, Shruti U. Rawal, and Mayur M. Patel

Abstract

Since the emergence of the concept of theranostics in 1998, the field has constantly evolved. With a unique amalgamation of diagnostic and therapeutic applications, theranostics has gained profound attention from researchers worldwide. More recently, researchers have attempted to augment the paradigm with the concept of "nanotheranostics," which offers multimodal medical and biomedical applications. "Nanotheranostics" are specially devised drug delivery systems/nanoformulations that comprise nanocarriers/nanoparticles for theranostics applications. "Nanotheranostics" confers special attributes to theranostics, thereby potentiating their efficacy. Spurred on by advances in material chemistry and nanoformulations, scientists have exploited distinctive electrical, magnetic and optical properties of several types of nanocarriers for theranostics applications. The present chapter discusses the nanocarriers of several types for diverse applications in disease state monitoring, treatment monitoring, personalized medicine, image-guided drug delivery, molecular imaging and pharmacogenomics. Besides offering the above-stated advantages, nanotheranostics can offer a safer and more efficient therapy to the patients, obviating redundant treatment and saving overall cost of therapy. Other aspects such as biological processes governing theranostics fundamentals, their applications in several diseases and medical conditions, regulatory aspects, commercial aspects and future perspectives have been discussed in the chapter.

Keywords

Theranostics · Nanomaterials · Diagnostics · Upconversion nanoparticles · Dendrimers

Nomenclature

CEO	Chief executive officer
Cy5	Cyanine 5
E. coli	*Escherichia coli*
MUC1	Mucin1
PDT	Photodynamic therapy
PEG	Polyethylene glycol
RBCs	Red blood cells
ROS	Reactive oxygen species
US	United States of America
USD	United states dollar
UV	Ultraviolet

S. Khot · S. U. Rawal · M. M. Patel (✉)
Department of Pharmaceutics, Institute of Pharmacy, Nirma University, Ahmedabad, Gujarat, India

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4.1 Introduction

The term "theranostics" was coined in 1998 by John Funkhouser to address the integrated science of therapy and diagnosis (Idée et al. 2013). Hence, theranostics can be ascribed as a multidisciplinary therapeutic paradigm, utilizing innumerable imaging, therapeutic and targeting agents, enabling real-time diagnosis and therapeutic drug monitoring in the future of personalized medicine.

Although the term theranostics was coined in late twentieth century, the use of theranostic formulations dates back to 1940s. Thus, the concept of theranostics is not entirely new to the field of medicine. It started with the use of radionuclides in diagnosis as well as in therapy. The use of radioactive iodine (I-131)-based formulation was first reported in 1941 by Saul Hertz for diagnosis and treatment of hyperthyroidism. In 1946, radioactive iodine was first ever to be reported for metastatic thyroid cancer therapy. Moreover, the biochemical moiety "Haem" was utilized in diagnostic imaging for cancer in the 1920s. Another biochemical moiety "phthalocyanine" was also used in positron emission-based diagnosis around the 1950s, whereas "porphyrin" was used as a contrast agent in magnetic resonance imaging around the 1980s. Since its inception till date, theranostics has been fostering remarkable tailored and targeted therapy.

Theranostics is most widely employed in the treatment of the majority of inflammatory diseases such as cardiovascular disease, neurodegenerative disease and cancer. Neurodegenerative diseases such as Alzheimer's, Parkinson's, epilepsy and Huntington's have been investigated for treatment with theranostics. The majority of cardiovascular diseases such as atherosclerosis, ischemia, hypertension, myocardial infarction and thromboembolism are potentially fatal and require precise treatment measures offered by theranostics nanomedicine. Further, life-threatening diseases such as cancer (breast, lung, brain, pancreatic and colon), multiple sclerosis and some of the autoimmune diseases are also reported to have been investigated for the employment of theranostics. The global theranostics market size was estimated at USD 6.22 billion in 2017 and is anticipated to gain significant traction over the coming years. Theranostic nanomedicine has offered promising and potential medical intervention by taking advantage of the high-payload nanoconstructs for both imaging and therapeutic function biomedicine (Bulte and Modo 2008). The advantages and disadvantages of theranostic delivery systems have been schematized in Fig. 4.1.

4.2 Fundamentals Governing Nanotheranostics

The use of nanotechnology in the field of medicine is emerging and expanding, since advances in scientific research spurred in the late twentieth century. Numerous examples of nanomedicines exist that have undergone thorough and extensive research from preclinical stage to clinical stage. Moreover, various nanocarrier-based systems have been extensively investigated such as liposomes, micelles, dendrimers and inorganic nanoparticles. These systems can be modified into less toxic, multifunctional and biocompatible nanoscaled vectors that have an enhanced biodistribution. In contrast to small molecules, theranostics nanomaterials render paramount potential in enhancing site-specific delivery of pharmacological agents. Moreover, multifunctionality of these theranostics agents depicts superior therapeutic efficiency and reduced adverse effects. Such diversified theranostics nanoplatforms are fabricated by combination of drugs and contrast agents for simultaneous imaging and therapy intended for active as well as passive targeted and controlled drug delivery. Engineering multifunctional theranostic nanoparticles present numerous challenges as mentioned below:

1. Limited choice of materials with inherent imaging and therapeutic properties which can be employed for designing such systems.
2. Inherent toxicity of individual components.
3. Lack of adequate storage and loading capacity as well as insufficient or inconsistent in vivo stability.

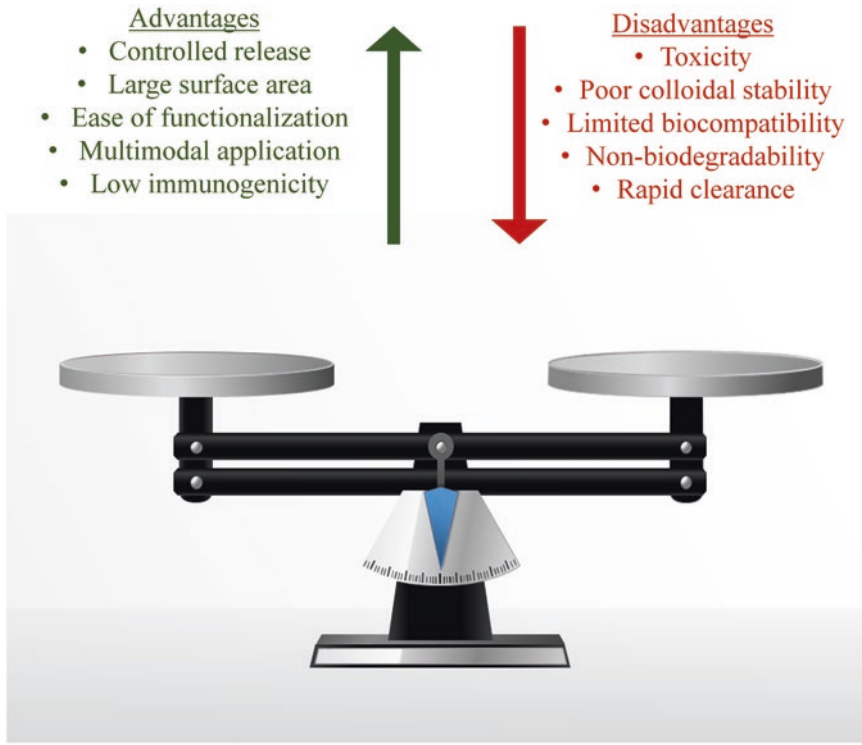

Fig. 4.1 Advantages and disadvantages offered by theranostic delivery systems

4. Complex fabrication process posing practical difficulties for industrial scalability and a high degree of variation in batch production.
5. Manufacturing cost incurred is often high.
6. Regulatory obstacles which impede clinical translation, development and progress.

Designing an ideal theranostics formulation requires a thorough screening and careful evaluation of drug and excipients. For example, a contrast agent for imaging in ideal conditions functions via faster binding to the target tissue and rapid systemic clearance, whereas drug delivery approach requires prolonged systemic circulation to achieve maximum uptake by target tissue. Similarly, physical characteristics and parameters of drug-loaded cargos (e.g. lipophilic drugs, lipophobic image contrast agent and polyionic nucleic acids) are subjected to considerable variation in order to achieve effective and optimum loading capacities by using different materials and strategies. Thus, it becomes difficult for any approach to provide a generalized theranostics platform for diverse applications. In order to integrate theranostics with nanotechnology, one must have a clear understanding of nanoscaled materials and their inherent physicochemical properties.

Nanoparticles can be defined as nanostructured constructs with particle size range of 10 nm to few hundred nanometres. In comparison with atoms or molecules, the nanoparticulate system possesses a significantly high surface area-to-volume ratio. Nanoparticulate systems are designed in particular fashion to enhance its magnetic, optical, electrical and immunological properties. Moreover, the technological advancements have enabled us to harness and alter their potential for utilization and widespread applications. These systems can be modulated into different sizes and shapes, surfaces, porosity and polarity. Theranostics nanoplatforms have been integrated with several stimuli-responsive agents, thereby enhancing their theranostics potential and providing a more accurate diagnosis as well as higher therapeutic efficiency and precision.

The stimulus can be classified as endogenous (e.g. pH, enzymes, hypoxia and redox) and exogenous (e.g. temperature, light, ultrasound, magnetic field). Furthermore, enzymes possessing inherent characteristics such as a high degree of relevance in several diseases in presence of precise and specific substrate selectivity and high catalytic activity are more likely and widely employed candidates for designing stimuli-responsive theranostics. Mechanism of catalysis mainly involves redox reaction with substrate leading to bond formation or cleavage. Numerous research studies have depicted widespread use of proteases, kinases, oxidoreductases and phosphatases in fabrication of stimuli-responsive systems. As a representative endogenous stimulus, enzymes are involved in a variety of key physiological processes and exhibit altered expression levels in many disease-associated microenvironments. For example, several enzymes such as proteases and phosphatases present high expression levels, which have been considered as biomarkers for the diagnosis and treatment of cancer, inflammation and neurodegeneration. A few examples of popularized commercial theranostics are listed in Table 4.1.

The following sections focus on various nanovectors, their applications in theranostics as well as their toxicity, pharmacokinetics, characteristics and compositions.

4.3 "Nanotheranostics": Nanomaterials for Theranostics Applications

4.3.1 Biomedical Imaging and Therapeutic Payloads

Imaging can provide valuable information about tissue composition, morphology and function, as well as quantitative descriptions of many fundamental biological processes. In recent years, biomedical imaging science has matured into a distinct and coherent set of ideas and concepts, and it has attained a position of central importance in medical research. In particular, numerous studies have been published on how imaging is evolving from qualitative visual depictions of anatomy into a science that contributes quantitative measurements of a variety of biomedical processes. Biomedical imaging is a useful tool for measuring the biodistribution, targeting and elimination of nanostructures in real time. This is especially needed at the whole organism level. In order to provide sufficient imaging contrast, biomedical nanodevices can be designed with reporting functions or moieties that provide a signal in conventional medical imaging modalities. These include gamma scintigraphy, magnetic resonance imaging (MRI), computed tomography (CT), positron emission tomography (PET)

Table 4.1 Commercial theranostic products

Brand name	Agent/system employed	Intent	Reference
Resovist®	Superparamagnetic iron oxide nanoparticles	MRI contrast agent in patients with liver diseases such as cirrhosis and hepatocellular carcinoma	Reimer and Balzer (2003)
Supravist®	Ultrasmall superparamagnetic iron oxide nanoparticles	MRI contrast agent in patients with multiple sclerosis and nephrogenic systemic fibrosis	Neuwelt et al. (2009), Engberink et al. (2010)
Neotect®	Technitium 99 m Depreotide	Used in oncotherapy for diagnosis and treatment.	Weiner and Thakur (2005)
Zevalin®	Yttrium-90 labelled ibritumomab and rituximab	Radioimmunotherapy for non-Hodgkin's lymphoma	Goldsmith (2010)
Bexxar®	Iodine-131 labelled tositumomab		
Folatescan™	Technetium-99 m etarfolatide or Technetium-99 m EC20	Treatment of rheumatoid arthritis, metastatic renal cell carcinoma and ovarian carcinoma	Naveed et al. (2004), Matteson et al. (2009), Marchetti et al. (2014)
Lipiodol®	I-131 poppy seed oil	Radiocontrast agent in hepatocellular carcinoma	Dumortier et al. (2014), Gallicchio et al. (2016)

and ultrasound (US) imaging. Additionally, digital radiography such as X-ray imaging has produced a spectrum of methods for interrogating intact 3D structure of the body non-invasively. A variety of new microscopies have also flourished, making use of novel phenomena such as nonlinear photon interactions and the sensing of atomic forces at surfaces. Of these, the functional imaging modalities are particularly useful given that nanomedicine targets processes at the cellular and molecular level.

Biomedical imaging involves the complex chain of acquiring, processing and visualizing structural or functional images of living objects or systems, including extraction and processing of image-related information. Several techniques are utilized for optical imaging such as near-infrared (NIR) fluorescence imaging (Hong et al. 2017; Hu et al. 2017), photodynamic therapy (Näkki et al. 2017) and photoacoustic and photothermal imaging therapy (Rong et al. 2015). Ultrasound-assisted imaging and therapy is another effective non-invasive method that can be utilized in designing potential theranostics (Emi et al. 2019). Moreover, nuclear chemistry is an effective and useful tool for imaging and therapy by utilizing radiolabeled nanoparticles. With the help of radio imaging techniques, these radiolabeled nanoparticles can be successfully employed for theranostics in cancer and other therapeutic applications (Liu et al. 2015; Dai et al. 2018). Theranostics nanomaterials are designed based on their physical and chemical properties such as optical, magnetic, thermal and radioactive properties.

In contrast to the conventional approach of using a single imaging tool, recently researchers are adopting multiple imaging approaches. The multi-imaging approach or multimodal approach has been extensively investigated in preclinical and clinical research. Few examples of multimodal approach are the use of a combination of imaging techniques such as MRI/PET, MRI/CT, MRI/PET/US, etc. Recently discovered photoacoustic imaging is yet another multimodal approach which serves as theranostics platform. This technique especially offers high-level precision and accuracy in imaging of endophytic tumours in contrast with other single modal imaging. Photoacoustic imaging possesses an ability to convert light signals into ultrasound, to yield a high contrast optical image and ultrasonic spatial resolution with deep tissue penetration in a single modality. Photoacoustic imaging has a wide range of applications in multiscale and multi-contrast visualization from cells to organs and anatomy to physiology. Moreover, innovations in photoacoustic techniques have rendered even better and advanced imaging, such as photoacoustic microscopy, photoactivated localization microscopy, stochastic optical reconstruction microscopy, confocal microscopy, photoacoustic endoscopy and CT (Liu et al. 2016).

The therapeutic payload includes a wide array of bioactives like the small molecules, peptides and proteins which are loaded with a carrier system for enhancing their efficiency through targeted delivery. Several such carrier systems are employed in preclinical and clinical research for enhancement in drug delivery. Inorganic nanostructures offer unique and desirable physicochemical properties and have been employed as molecular payloads for peptide delivery (Bertucci et al. 2018). Magnetic nanoconstructs have been employed as multifunctional therapeutic payloads for all in one cancer therapy (immune, thermal, chemo and radiotherapy). Such magnificent multifunctional payloads could address and overcome the challenges offered by conventional cancer therapy leading towards a new paradigm in modern cancer theranostics (Datta et al. 2016). Similarly, porous silicon nanoconstructs depict excellent materialistic properties and advanced theranostics applications for incorporation of therapeutic payloads (Kumeria et al. 2017). Furthermore, Janus-like nanoparticles have been synthesized and investigated in cancer treatment. These nanoparticles comprised of magnetite and gold nanohybrids exhibiting dual nature and were found superior as compared to pre-existing commercial MRI contrast agents (Efremova et al. 2018). Other than inorganic nanomaterials, several other bio-inspired materials are also under investigation as potential theranostics agents. Antibody-drug conjugates have been employed as potential tumour cell-specific targeted payloads in cancer theranostics (Miller et al. 2018). Newer therapeutic payloads have been designed using non-pathogenic *E. coli*. The novel designs

have shown high efficiency and excellent biocompatibility as drug delivery systems (González-Prieto and Lesser 2018). Moreover, RBCs have also been utilized as multifunctional bio-inspired cargos as potential cancer theranostics agent. The multifunctionality and high payload capability of RBC can render multimodal cancer therapy. Additionally, these cargos have low off-target toxicity and excellent biocompatibility and safety in simultaneous monitoring and treatment (Wu et al. 2015). Bio-inspired nanomaterials will continue to gain popularity and significance because of their advantages in circumventing the biological barriers, which are huge hurdles for use of conventional nanovectors in drug delivery (Evangelopoulos et al. 2018). The role of theranostics in cancer therapy has been exemplified in Fig. 4.2.

4.3.2 Nanotheranostics Carriers

Various nanocarriers that have been employed for diagnostic and therapeutic application are discussed in the present section.

4.3.2.1 Polymeric Nanocarriers

Polymeric Micelles

Polymeric micelles are composed of units of natural or synthetic polymers which condense and precipitate under suitable process conditions to give nanospheres or nanoparticles. Upponi et al. (2018) described a polymeric nanoformulation comprising of PEG and phosphatidylethanolamine for diagnosis and treatment of cancer. The prepared micellar formulation was utilized for the loading of hydrophobic and water-insoluble paclitaxel and superparamagnetic iron oxide nanoparticles. The former is a functional chemotherapeutic agent, and the latter one is used as an MRI contrast agent. These polymeric micelles were found to be stable with minimum interaction between the loaded therapeutic and diagnostic agents. Moreover, the developed formulation depicted significant retention in magnetic properties as well as enhanced tumour cell apoptosis in murine breast cancer and melanoma as compared to single-agent-loaded micelles. Furthermore, the development of such nanotheranostics displays a high degree of synergism, enabling it to be more efficient in treatment as well as real-time analysis in contrast to conventional ex vivo diagnosis. Such nanosystems can be further integrated with targeted therapies such as multimodal photodynamic therapy, magnetic hyperthermia and radiotherapy.

Polymer-Drug Conjugates

Nagel et al. (2018) have described stimuli-responsive cleavable motif-based nanoscaled polymer-drug conjugates for cancer therapy. The authors have developed a novel theranostics system triggered by cell-mediated stimuli. The

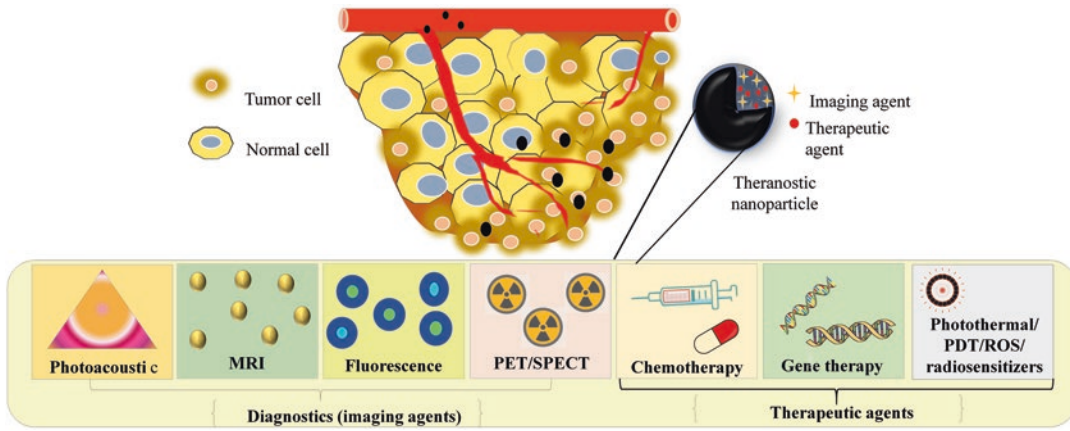

Fig. 4.2 Role of theranostics in cancer therapy

system was integrated by embedding two different linker molecules in dendritic polyglycerol matrix, i.e. a pH-responsive and enzyme-responsive linker for aldoxorubicin and doxorubicin, respectively. Moreover, the prodrug was conjugated with the thiol functional group intended for interaction with the cysteine residue of albumin to prolong its circulation and controlled drug release in the tumour microenvironment. The developed system was activated optically at the excitation wavelength of 490 nm, resulting in emissions at 590 nm (for doxorubicin) and 670 nm (for indidocarbocyanine). Both drug and dye conjugated to polymer depict inherent fluorophoric properties. In order to enhance the efficiency of the system, the donor fluorophore (doxorubicin) and acceptor fluorophore (indidocarbocyanine) were spaced 10 nm apart. Subsequently, the stimuli-responsive linker was selected in a particular manner to render drug conjugation and attachment for quencher fluorophore in close proximity to the drug. Furthermore, in vitro release studies of doxorubicin carried out using fluorescence microscopy and flow cytometry depicted enhanced and targeted drug release as compared to free drug. The authors reported superior performance of the pH-responsive system vs. enzyme-responsive one, due to the occurrence of premature drug release when acted upon by extracellular proteases. This had a pronounced effect on the treatment of a multidrug-resistant cell line where an intracellular drug release is crucial to overcome the resistance mechanisms. Therefore, the developed system was successful in the treatment of cancer and provided targeted and controlled drug release in response to tumour microenvironment making it a potential theranostics candidate for future cancer therapy.

Polymeric Nanogel

Polymeric nanogel is a broader term to describe the novel delivery system which incorporates polymers via cross-linking into a nanogel system. Gyawali et al. (2018) described a novel biodegradable polymeric nanogel-loaded doxorubicin for anticancer treatment. The novel synthesized polymer possessed inherent photostability and fluorescent properties. The theranostics potential of the prepared polymer was enhanced by surface functionalization with cyclic arginine-glycine-aspartic acid (cRGD) peptide for targeted and pH-dependent release in the tumour microenvironment. The authors synthesized photocross-linkable photoluminescent polymer by using biodegradable monomers such as citric acid, PEG, L-cysteine and maleic acid. Moreover, the prepared nanogels displayed excellent biological stability, biocompatibility along with strong fluorescent properties and enhanced uptake by the tumour cell. Fluorescence-guided imaging depicted cytoplasmic accumulation of doxorubicin in prostate cancer cells which resulted in augmented cell death. In conclusion, this novel synthesized polymer can be used as a potential theranostics platform for simultaneous tumour diagnosis and real-time pH-responsive drug monitoring. Chambre et al. (2018) described the synthesis of a novel polymeric nanogel obtained via cross-linking of reactive copolymers. Furthermore, drug conjugation was achieved via carbamate linkage and embedded in thiol-maleimide-functionalized PEG. The cRGD peptide was employed for surface functionalization of developed nanogel intended for targeted delivery of doxorubicin. The developed polymeric nanogel, which is comprised of a self-assembled cross-linked copolymer, was thus intended for thermo-responsive anticancer therapy. The functionalized maleimide-thiol PEG was responsible for the cross-linking ability of the nanogel. Succinimidyl-dicarbonate was employed to render carbonate functionalized doxorubicin-conjugated polymer, responsible for forming an acid labile carbamate linkage in response to drug release in the tumour microenvironment. Furthermore, the Cy5 dye was added to the nanogel system to render fluorescence imaging properties. In conclusion, the developed system depicted enhanced drug release and superior uptake as well as cytotoxicity in L929 fibroblast and MDA-MB-231 breast cancer cells in vitro. It can be envisioned that facile fabrication and multifunctionalization of these reactive nanogels offer a modular platform that can be configured as a theranostics agent for addressing challenges in conventional therapy of various diseases.

4.3.2.2 Lipid Nanocarriers

Liposomes

Liposomes are bilayered phospholipid vesicles that are formed spontaneously in the presence of aqueous solutions. Zhang et al. (2018) described a liposomal system loaded with hypoxia-activated chemotherapeutic prodrug combined with photodynamic therapy for anticancer treatment. The authors demonstrated the fabrication of 2-nitroimidazole-conjugated PEG-based theranostic liposome. Tirapazamine prodrug, lipophilic chlorine 6 and miRNA 155 as gene probe were encapsulated in the developed liposomal system. The gene probe was labelled with a fluorescent dye and quencher, which in the absence of target shows quenching of fluorescence by the dye in close proximity and upon target hybridization resulted into the separation of dye producing fluorescence imaging. Chlorine 6 renders photosensitizer functionality which was activated upon laser irradiation at 670 nm producing photodynamic therapy and severe hypoxia. This triggered the liposome disassembly, thereby activating tirapazamine prodrug to produce a cytotoxic anticancer effect. Encapsulated gene probe yielded enhanced fluorescent imaging along with differentiating cancer cell uptake vs. normal cells. The developed liposomes depicted enhanced in vitro and in vivo performance by significantly improved antitumor activity compared to conventional PDT. Thus, fabrication of nano-liposomal theranostics platform may contribute to the design of a hypoxia-responsive multifunctional system for tumour diagnosis and hypoxia-activated chemotherapy combined with PDT for synergetic therapy, holding great potential for future cancer therapy.

Solid Lipid Nanoparticle (SLN)

Shen et al. (2019) described a combination of magnetic hyperthermia and chemotherapy-based theranostics nanocarriers for oral anticancer treatment. The authors demonstrated the fabrication of doxorubicin and superparamagnetic iron oxide nanoparticle-loaded SLN theranostic for colon targeted delivery. These SLNs were further functionalized using folic acid/TPGS and octadecanol-modified dextran via layer-by-layer encapsulation. This developed system provided hyperthermic action of superparamagnetic iron oxide nanoparticles and chemotherapeutic effect of doxorubicin upon activation by the high-frequency magnetic field in orthotopic colon cancer. Folic acid-decorated doxorubicin and superparamagnetic iron oxide nanoparticle-loaded SLN encapsulated in dextran shell demonstrated successful evasion from systemic uptake, thereby enhancing local delivery in the colon. Employing folic acid/TPGS on to SLN allowed selective uptake by folic acid overexpressed cancer cells. The literature review revealed the presence of folate receptors in the small intestine as well, thereby limiting the colon targeting action. Hence, modified dextran was employed to overcome the challenge of preventing intestinal uptake. Furthermore, selective degradation of dextran shell was found upon the action of dextranase secreted in the colon. This functionalization yields highly effective and targeted delivery in colon cancer. Therefore, the developed system was highly efficient in providing a synergistic anticancer effect and a significant reduction in off-target toxicity. The system also depicted enhanced cell uptake and tumour growth inhibition in vitro and in vivo via magnetothermal and chemotherapeutic combination therapy.

Nanostructured Lipid Carriers (NLC)

Fernandes et al. (2018) described doxorubicin and docosahexaenoic acid-loaded NLCs for targeted cancer delivery. The in vitro and in vivo performance depicted superior activity as compared to free drug. Moreover, technetium-99 m labelling was employed for enhanced theranostics application of developed NLCs. Scintigraphy and biodistribution studies of NLC were performed in 4 T1 breast cancer cell-bearing mice depicting the enhanced anticancer activity of encapsulated doxorubicin compared to its free form. Radiolabelling enabled precise imaging potential of preferential nanoparticle uptake by tumour cells. Furthermore, the developed system depicted prolonged circulation, high therapeutic payload and superior anticancer effect.

Docosahexanoic acid and Doxorubicin co-loaded NLCs displayed synergistic and augmented antitumor effects. Additionally the system was found to produce reduced off-target toxicity. Therefore, the developed system may serve as a potential theranostics candidate for real-time drug monitoring and diagnostic imaging in breast cancer.

Lipid-Polymer Hybrids

Lipid-polymer can be defined as a combination system involving the use of polymer with predetermined function in lipid nanosystems. Huang et al. (2019) described Pt(IV) prodrug-loaded lipid-polymer nanohybrids for treatment of ovarian cancer. The nanohybrid system is comprised of the liquid core of perfluorohexane, a lipo-polymer shell of PLGA-PEG and DSPE-PEG-Pt(IV) as well as cRGD peptide as targeting ligand. The perfluorohexane core was employed as an ultrasound contrast agent for enhanced and real-time imaging. The developed nanohybrids displayed multifunctionality and reduction in sensitive tumour targeting. The cRGD peptide was conjugated to the nanohybrid system for enhanced targeted delivery. The developed system displayed enhanced US imaging, drug release, cell uptake, cytotoxicity and cell apoptosis in vitro and in vivo. Thus, the developed hybrid can serve as a highly efficient theranostics platform for the treatment of ovarian cancer. You et al. (2018) described a pH-responsive system based on reactive oxygen species (ROS) triggered under NIR irradiation for cancer therapy. The authors demonstrated the fabrication of succinic peroxide-conjugated PLGA with Fenton-activated Pt/Fe_3O_4 lipo-polymersome. The presence of Fenton reactive species triggers the production of OH radicals as a source of ROS in cancer therapy. The developed system was rapidly internalized with further depolymerization leading to the formation of loose structures disintegrated with an increase in temperature as a consequence of NIR irradiation. Consequently, the release of ferrous ions and dissociate succinic peroxide triggered the formation of OH radicals in response to NIR irradiation when exposed to the tumour microenvironment. Cisplatin-loaded system depicted enhanced antitumor efficacy in vitro and in vivo. Furthermore, the developed system displayed multifunctionality, excellent biocompatibility, reduced off-target toxicity, high yield of ROS and enhanced uptake and accumulation in tumour cells. Moreover, the developed system also demonstrated excellent in vitro and in vivo performance in suppressing MCF-7 tumour cells. Thus, fabrication of lipo-polymersome nanohybrids can serve as a potential theranostics platform towards clinical translation for cancer therapy (Huang et al. 2019).

4.3.2.3 Dendrimers

Dendrimers are highly branched, star-shaped macromolecules with nanometer-scale dimensions. Dendrimers are defined by three components: a central core, an interior dendritic structure (the branches) and an exterior surface with functional surface groups. Alibolandi et al. 2018 described poly(amidoamine) dendrimer-based multifunctional nanotheranostics platform. Gold nanoparticles and curcumin were loaded onto the poly(amidoamine) dendrimer and conjugated with MUC1 aptamer for selective and enhanced tumour targeting. The developed system was intended for CT imaging and drug delivery to C26 tumour cells in vitro and in vivo. Moreover, MUC1 aptamer was conjugated via thiol functionalization to heterofunctional PEG. This developed nanosystem displayed marked targeting to MUC1 in HT29 and C26 cancer cell. Furthermore, the system also depicted high cell uptake, cytotoxicity and enhanced anticancer efficacy. In conclusion, the developed nanotheranostics system depicts good X-ray attenuation and is a desirable probe for CT imaging while demonstrating high therapeutic index against colorectal cancer. Jędrzak et al. 2019 described the synthesis of poly(amidoamine) functionalized magnetic nanoparticles encapsulated with polydopamine for advanced cancer therapy. Fifth-generation nanohybrids were employed for combination photothermal and chemotherapy in liver cancer treatment. The developed nanoparticles displayed no toxicity in healthy cells and exhibited strong photothermal properties. The developed system demonstrated a high degree of drug loading and the synergistic

additive effect of photothermal therapy as well as chemotherapy. In vitro and in vivo studies depicted apoptosis-induced cell death instead of necrosis, thereby confirming highly efficient and versatile nature of the developed system. Moreover, the developed system displayed excellent MRI contrast properties. Overall, the functionality of dendrimers has been extended by merging them with magnetic nanoparticles resulting in multifunctional hybrid nanostructures making them a promising smart drug delivery system for cancer therapy.

4.3.2.4 Inorganic Nanocarriers

SPIONs and Magnetic Nanocarriers

Superparamagnetic iron oxide nanoparticles are iron oxide nanoparticles which have different electromagnetic properties due to their nanosize, a phenomenon called superparamagnetism. Gholami et al. (2019) described the fabrication of doxorubicin and superparamagnetic iron oxide nanoparticle-loaded polyarginine/chitosan nanoparticles. The developed system was fabricated using ionic gelation loaded with biodegradable chitosan for dual application, i.e. diagnosis and therapy. In vitro release studies depicted burst release from the developed system in an acidic environment, hence exhibiting pH-dependent release behaviour suitable for release in the tumour microenvironment. Moreover, flow cytometric analysis and fluorescence microscopy demonstrated rapid internalization of the developed system into the tumour cells. Consecutively, the in vitro uptake was corroborated by drug accumulation in intracellular space of C6 glioma cells using MRI. Additionally, the developed system depicted excellent biocompatibility, long-term stability and safety along with cytotoxicity against cancer cells. In conclusion, the developed system may serve as a promising theranostics platform for glioblastoma intervention in futurized clinical applications. Abedin et al. (2018) described essentiality of functionalized inorganic nanoparticles in nanomedicine to address the issue of dispersibility in physiological environments. The authors demonstrated modulation of colloidal stability of gold-iron oxide nanoparticles by employing a polymer coating of poly-L-lysine. The polymer-coated inorganic nanoparticles were found to remain as a stable dispersion in aqueous and physiological media, thus causing rapid internalization of nanoparticles in cells. The multifunctional NIR-responsive gold-iron oxide nanoparticles were intended for simultaneous imaging and photoactivated hyperthermic treatment of breast cancer cells. Surface-coated inorganic nanoparticles demonstrated the formation of a physical barrier around inorganic nanoparticles as a function of the polymer coating, thereby imparting stability and preventing its aggregation. The physicochemical properties of inorganic materials can render a multimodal nanoplatform, e.g. gold nanoparticles possess surface plasmon resonance and superparamagnetic properties which can be successfully employed for photothermal ablation as well as enhanced MRI contrast, respectively. The developed nanoparticles, which were investigated in BT-474 and MDA-MB-231 breast cancer, depicted enhanced cell uptake in NIR-assisted photothermal therapy. Moreover, the developed nanoparticles were able to promote and enhance tumour growth inhibition more significantly as compared to nanoparticles without NIR activation. In conclusion, the developed nanoparticles displayed excellent optical, magnetic and therapeutic properties by integrating diagnostic and therapeutic functions into a single multimodal nanotheranostics platform for translational cancer therapy.

Quantum Dots

Quantum dots are tiny particles or nanocrystals of a semiconducting material with diameters in the range of 2–10 nanometres. Quantum dots display unique electronic properties, intermediate between those of bulk semiconductors and discrete molecules, which are partly the result of the unusually high surface-to-volume ratios for these particles. The most apparent result of this is fluorescence, wherein the nanocrystals can produce distinctive colours determined by the size of the particles. Chang et al. (2019) described multifunctional quantum dot-based theranostics nanoformulation rendering diverse platform to address

heterogeneity in cancer therapy. The authors demonstrated the development of a hybrid peptide for simultaneous diagnosis and cancer therapy. The research study involved isolation of two functional peptides A and B from *E. coli* and their conjugation with streptavidin-loaded quantum dots and magnetic nanoparticles, respectively. Furthermore, these functional peptides were coupled by promoting interaction between appropriate domains of both peptides. The developed hybrid system is comprised of streptavidin-loaded quantum dots, magnetic nanoparticles and targeting ligand designed for the treatment of HER2-positive breast cancer. The developed multifunctional hybrid system was efficient in the detection and inhibition of tumour growth of HER2-positive breast cancer. The developed hybrid system was equipped with ZH2 affibody which enabled specific targeting of HER2 receptor. To achieve optimum therapeutic efficacy, the developed hybrid system was employed for simultaneous quantum dot-assisted fluorescence imaging and magnetic hyperthermia for breast cancer treatment. The developed hybrid system is simple and flexible equipped with tunable modules rendering protein-protein interaction domains for lowering the immunogenicity. In conclusion, the developed hybrid system is highly useful in numerous biological applications serving as a potential theranostics platform in the development of an advanced bioassay for early cancer detection.

Metallic Nanoparticles

Nanoparticles are prepared from metals like iron, silver, gold, cobalt, zinc, etc. by various physical and chemical techniques to get nanoparticles in size range of 5–20 nm. Sakr et al. (2018) have described the development of a potential nanotheranostics system comprising of I-131-doped silver nanoparticles functionalized using PEG. The authors have integrated cancer therapy silver nanoparticles and radiolabelling. The nanoparticles were fabricated using a one-step synthesis of PEG-encapsulated silver nanoparticles doped with I-131. The developed system depicted excellent radiolabelling yield (~98%) along with significant stability in aqueous and physiological media in vitro. The developed system depicted temperature-sensitive behaviour and hence was administered in cold condition. Moreover, the developed system was safe and biocompatible and showed reduced off-target toxicity. The developed system depicted a high amount of radioactivity in tumour-bearing mice with enhanced tumour uptake upon post-intravenous as well as intratumoural injection. Thus, the developed system may serve as great potential in cancer theranostics. Liu et al. (2018) described a novel theranostics nanoconstruct comprising of hyaluronate-based cationic bovine serum albumin-encapsulated gold nanocluster for targeted drug delivery in cancer therapy. The authors demonstrated modulation of particle size by altering the hyaluronate to cationic bovine serum albumin-encapsulated gold nanocluster which was investigated for its targeting and pharmacokinetic potential. This preliminary screening then led to the selection of the developed system with size of 200 nm based on optimal EPR effect. Moreover, the developed system possessed red fluorescence providing real-time imaging and inherent drug binding sites. Therefore, the developed system was further utilized for loading of indocyanine green dye and lipophilic paclitaxel providing photothermal and chemotherapy, respectively, and nitric oxide for modulating the tumour microenvironment and enhancing drug delivery. Hyaluronate incorporation into the developed system imparted protection to charged nanoparticles, in turn, prolonging its systemic circulation and reduced off-target toxicity. Furthermore, the developed system depicted active targeting ability and facilitated penetration due to size reduction triggered by a degradation of hyaluronate shell in the tumour microenvironment. The developed system depicted high accumulation in breast cancer cells. Consequently, the developed system demonstrated in situ suppression of tumour growth (~95%) as well as lung metastatic growth inhibition (~88%). In conclusion, the developed system was safe and biocompatible intended targeted delivery and sufficient suppression of breast cancer.

Upconversion Nanoparticles

Jin et al. (2019) described a facile fabrication of NIR-assisted theranostics nanoconstructs via encapsulation of upconversion nanoparticles and a luminogen {2-(2,6-bis((E)-4-(phenyl(40-(1,2,2-triphenylvinyl)-[1,10-biphenyl]-4-yl) amino)styryl)-4H-pyran-4-ylidene)malononitrile} (TTD) within an amphiphilic polymer-based nanohybrid system. To obtain cancer cell targeting, the developed system was further conjugated with cRGD peptide to yield hybrid nanoparticles. A class of fluorogens has emerged to serve as an efficient and potential fluorescent material useful in theranostics applications. These fluorogens exhibit aggregation-induced emission properties, which can be described as non-emissive materials in appropriate solutions but can render high emission properties upon aggregation. Mechanism of aggregation can be explained via restricted intramolecular rotations that prevent dissipation of energy through non-radiative channels. Therefore, aggregation-induced emission-based photosensitizer has been employed widely as key materials for single-unit multimodal imaging and photodynamic therapy. Upconversion nanoparticles possess the ability to harness NIR frequency and upconvert into higher frequency such as visible or UV light. Therefore, selection of appropriate upconversion nanoparticles having similar emission spectra to that of aggregation-induced emission photosensitizer can render a potential platform for NIR-assisted nanotheranostics in the treatment of deeply situated tumours. The authors have discussed the encapsulation of hydrophobic luminogen (TTD) and upconversion nanoparticles into a biocompatible lipid-PEG polymer hybrid surface decorated with cRGD peptide for targeted action. This developed system depicted NIR-assisted multifunctional probes intended for photodynamic therapy in cancer cells. Furthermore, the developed system depicted efficient generation of ROS upon NIR excitation in the presence of thick tissue. Additionally, the developed system depicted highly efficient targeting and significant in vitro anticancer activity against MDA-MB-231 breast cancer cells. Moreover, in vivo studies depicted enhanced accumulation of developed system and significant tumour growth inhibition. Also intravenous injection of the developed system could illuminate the tumours and induced significant apoptosis in tumour cells. The developed system showed excellent photostability and was able to maintain its fluorescent properties for a longer duration (1 month). Theranostic probes composed of a combination of upconversion nanoparticles and photosensitizers may serve as a platform for NIR-assisted imaging and phototherapy of deeply situated tumors. Wang et al. (2019) described precision-based theranostics nanoplatforms for image-guided tumour-targeted delivery of chemotherapeutic drugs. Lanthanide-doped upconversion nanoparticles are attractive systems for the design of theranostic platforms which serve as a potential candidate in laser components, NIR probes, low-background bioimaging and solar energy conversion. The intrinsic NMR properties of gadolinium (Gd) ions can be employed for multimodal imaging. Furthermore, rare-earth co-doped elements ytterbium (Yb^{3+}) and erbium (Er^{3+}) can offer absorption of NIR excitation photon and emission upconversion luminescence, respectively, which can be applied to fluorescence labelling and luminescence resonance energy transfer. The developed nanoplatform comprised of $Gd/Yb^{3+}/Er^{3+}$ upconversion nanoparticles and gold nanodots encapsulated bovine serum albumin in a layer-by-layer manner which was further conjugated to folic acid. This developed nanohybrid system was then successively employed for loading of doxorubicin. The upconversion nanoparticles provided photothermal effect along with NIR conversion and depicted excellent luminescent properties, X-ray attenuation and photothermal ablations. Moreover, bovine serum albumin was rendered as a template for doxorubicin binding, thereby enhancing its anticancer efficacy via photothermal therapy. The developed system was efficient in the delivery of doxorubicin within the tumour microenvironment, thereby reducing the off-target toxicity during treatment regime. Meanwhile, in vivo anticancer efficacy was improved by the pH-responsive release of doxorubicin in association with NIR excitation-induced heat. The developed system was highly

effective in rendering multimodal imaging and potent anticancer response as well as tumour growth inhibition via deep penetration ability of photothermal therapy. The bovine serum albumin and folic acid coating provided prolonged circulation and a replacement for conventional surfactants to further render non-toxic, biocompatible and safe theranostics nanoplatform for in vivo cancer therapy. In conclusion, the development of such nanohybrids may serve as potential novel theranostics strategies which can be employed in simultaneous multifunctional diagnosis and therapy.

Silica and Other Nanoparticles

Su et al. (2019) described the fabrication of functional theranostics mesoporous silica-coated gold nanostars as combination photothermal therapy and chemotherapy in the treatment of cancer. The authors demonstrated the synthesis of mesoporous silica-coated gold nanostars using sodium hydroxide etching. The silica-coated nanoparticles were functionalized by grafting PEG and further loaded with doxorubicin. The developed system displayed good dispersibility in aqueous and physiological media. Moreover, the developed system depicted good drug-loading capacity and pH as well as light-responsive drug release. Upon NIR excitation, the developed system depicted excellent photothermal effects. Also the combination therapy in HeLa and cervical cancer cell lines consequently displayed superior anticancer efficacy than chemotherapy or photothermal therapy alone. The developed nanocomposites depicted excellent biocompatibility with low toxicity. In conclusion, the developed nanocomposite system serves as a multimodal theranostics platform for treating cancer. Victor et al. (2018) described the fabrication of calcium phosphate-based ceramic nanoparticles present as a unique drug delivery system. The developed system renders functional, biocompatible and biodegradable properties in vivo. The in vitro studies depicted rapid internalization of nanoparticles. Furthermore, the developed system depicted prolonged systemic circulation at physiological pH with low systemic toxicity. Moreover, the developed system was doped with neodymium encapsulated with alginic acid for pH-responsive drug release. Acetylsalicylic acid was loaded onto the developed functionalized nanocarrier for orally administered colon targeted delivery. The drug-loaded nanoparticles of 20–40 nm in size displayed negative surface charge, thereby facilitating simultaneous imaging and pH-responsive drug delivery. In conclusion, the lanthanide-doped calcium phosphate-based nanotheranostics may serve a potential for simultaneous imaging and therapy in the treatment of solid tumours. Cipreste et al. (2018) described the fabrication of hydroxyapatite nanoparticles doped with an array of radionuclides intended for theranostics applications in the treatment of various types of cancer. The authors demonstrated the synthesis of functionalized nanocomposite comprised of hydroxyapatite and CuO (known as tenorite) for PET imaging and simultaneous diagnosis and treatment of osteosarcoma. Copper serves as a potential candidate for modulation of hydroxyapatite nanoparticles to yield certain desirable theranostics properties. Activation of this metal by a neutron flux can produce 64Cu, a positron and beta radiation. The emitted beta radiation can be employed to kill cancer cells, and the positron radiation could be used to generate diagnostic images in PET systems. ^{64}Cu and ^{32}P were the two radionuclides, which were doped to the prepared nanocomposites, and upon activation inside the hydroxyapatite matrix can produce desirable theranostics material. Moreover, the developed system was found to stable and biocompatible in physiological conditions and serve as an excellent theranostics agent against osteosarcoma. The developed system was conjugated with folic acid to render active targeting to folate-overexpressed osteosarcoma cells. Wyszogrodzka et al. (2018) described a facile fabrication of novel metal-organic framework Fe-MIL-101-NH2 as a theranostics platform for antituberculous drug therapy. Several nanosized iron-based metal-organic frameworks (MIL-88A, MIL-89 and MIL-101-NH2) have been synthesized as drug cargos rendering good MRI contrast properties. The developed system was able to depict multifunctionality, significant drug loading, excellent

MRI contrast agent and low level of toxicity. The developed hybrid metal-organic frameworks, which were loaded with isoniazid and were investigated for its cytotoxicity against fibroblasts L929, depicted enhanced accumulation inside the cells. The proposed drug delivery system can also serve as the MRI contrast agent. Dissolution studies of the developed nanohybrids depicted an extended-release pattern. In conclusion, the developed system was found suitable for the extended-release inhalable system in drug delivery of isoniazid along with monitoring of drug-loaded hybrid system distribution within the lung tissue. Theranostics is widely employed for cancer treatment, but numerous other examples do exist for effective treatment and local drug delivery. The developed system demonstrates that Fe-MIL-101-NH2-based metal-organic framework can serve as an effective theranostics carrier for first-line antitubercular treatment with isoniazid. Additionally, MRI imaging of the developed system suspended in HPMC demonstrated the contrast ability of the novel theranostics platform. The proposed features such as efficient drug delivery and excellent imaging properties, in combination, describe a single all-in-one carrier system allowing it to be classified as a potential theranostics agent for tuberculosis treatment.

4.3.2.5 Carbon-Based Nanomaterials

Fullerenes Nanoparticles

Fullerenes were first discovered back in 1985 by Harold Kroto and his group at the University of Sussex, England. Kroto described fullerene as large and hollow spheroidal molecule composed of 60 or more carbon atoms. Fullerenes are produced chiefly by the action of arc discharge between carbon electrodes in an inert atmosphere. Misra et al. (2018) described functionalized C60 fullerenes as a potential theranostics platform in drug delivery of antiviral drugs employed for HIV treatment. The derivatives of fullerene C60 exhibited inhibition of HIV proteases via complex formation, among which dendrofullerene was found to have the highest inhibitory activity. Interestingly, amino acid-modified fullerene C60 was found to inhibit HIV replication in humans. Moreover, C60 fullerene has been utilized for potential medical application based on its photo-excitable properties. N-vinylpyrrolidone-functionalized C60 can form highly hydrophilic copolymer complex for photodynamic therapy. Fullerene C60 is also an inherent antioxidant as a consequence of its unique chemistry. Functionalization of fullerenes has been investigated in numerous activities such as radioprotective drug delivery, MRI contrast and photodynamic and gene therapy. Furthermore, researchers have discovered that under specific conditions, these fullerenes possess the ability to stimulate the generation of ROS and killer cells. He et al. (2019) developed a multifunctional contrast agent intended for simultaneous imaging and synergistic high-intensity focused ultrasound-assisted therapy. The authors described fabrication of perfluorohexane-encapsulated fullerene nanosphere, which was subsequently employed in US/CT dual-modality and high-intensity focused ultrasound ablation therapy. The developed system significantly enhanced integrated US/CT imaging along with enhanced high-intensity focused ultrasound ablation in dissected livers. In conclusion, the developed composite nanospheres demonstrate potential theranostics application as a multifunctional contrast agent for dual-modal biological imaging and highly efficient synergistic imaging-guided high-intensity focused ultrasound ablation.

Carbon Nanotubes

Carbon nanotubes can be classified as a subcategory of fullerene derivatives with similar and widespread application in the medical, biomedical and pharmaceutical field. Structurally carbon nanotubes are cylindrical nanoconstructs having a high length to diameter ratio. Two functional carbon nanotubes have been described for its use in biomedical field, viz. single- and multi-walled carbon nanotubes. Like fullerenes, carbon nanotubes also possess numerous optical fluorescence properties making them a potential material in photothermal cancer therapy. Fiegel et al. (2018) described the fabrication of carbon-

based nanotubes for designing potential theranostics nanoconstructs. The developed nanoconstructs based on carbon nanotubes depicted high drug loading capacity with combination of photothermal therapy and imaging property. To overcome the poor hydrophilicity of carbon nanotubes, mesoporous silica shell was grafted which was further encapsulated with human serum albumin to form nanofilms via isobutyramide cross-linking. Curcumin and camptothecin were loaded onto the developed system. The porous silica rendered sites for drug loading. Thus, the developed nanocomposite system was found to be biocompatible and safe with reduced side toxicity. Hence, such systems can be utilized in the future for phototherapy and NIR-assisted drug delivery. Such novel nanocomposites are expected to be very promising new theranostics systems ensuring drug delivery, imaging and photothermal properties.

Carbon Nanodots

Carbon nanodots belong to a novel class of small theranostics nanoplatforms with size range below 10 nm, capable of exhibiting excellent optical and non-toxic properties. These unique properties of carbon nanodots are utilized in designing of ideal platforms for multifunctional cancer targeting. Numerous applications of carbon dots in cancer theranostics have been reported during the past decade. Ortega-Liebana et al. (2019) described the fabrication of nitrogen-doped carbon nanodots, which were employed as dual-modal theranostics, rendering NIR-assisted imaging and photodynamic therapy. The developed nanodots were rapidly internalized inside tumour cells via selective uptake and did not show cytotoxicity prior to NIR irradiation. The developed nanodots depict excellent photodynamic properties, along with highly efficient simultaneous imaging as well as cancer therapy. Cancer therapy was found to be efficient and displayed good luminescent properties upon NIR excitation which triggered in situ ROS generation. This ROS generation induced cell apoptosis in U251 cells in vitro visualized by flow cytometry.

Graphene Nanoparticles

Usman et al. (2018) described the fabrication of graphene oxide-based theranostic nanoconstructs for cancer imaging and therapy. The graphene oxide was employed for loading of anticancer protocatechuic acid and gadolinium nitrate hexahydrate as an MRI contrast agent. Gold nanoparticles were also employed as a contrast material for diagnosis. The graphene oxide nanosheets were conjugated with protocatechuic acid which was further conjugated to gadolinium nitrate. A similar process was followed to obtain gold-coated graphene oxide nanosheets. The developed system depicted significant cytotoxicity and excellent MRI contrast properties. The cytotoxicity studies depicted significant cytotoxicity in human liver hepatocellular cancer cell lines, but apparently, no significant cytotoxicity was observed in fibroblast cell lines. Moreover, the gold-coated nanosheets depicted superior contrast activity as compared to gadolinium-coated nanosheets. Therefore, the developed system has good prospects of serving as a future theranostics platform for cancer chemotherapy and diagnosis. Shervedani et al. (2018) described fabrication of novel graphene-based theranostics nanoplatform for cancer therapy. The authors demonstrated the synthesis of a multifunctional hybrid system comprising of partially reduced graphene oxide functionalized by polydopamine. This reduced graphene-polydopamine system was further grafted onto bovine serum albumin which was decorated with diethylenetriaminepentaacetic acid-Mn (II) employed as a diagnostic agent and loaded with chemotherapeutic agent methotrexate. In vitro studies depicted enhanced drug release and cell uptake which can be accounted to bovine serum albumin facilitating internalization and uptake.

4.4 Conclusion and Future Perspectives

To summarize briefly, the design of current and future theranostics deals with three important components, viz. imaging/diagnostic agent, ther-

apeutic moiety and a targeting agent. All three components mentioned above have been extensively investigated in the design, development and evaluation of tailored theranostics applications. Great achievements have been made in the past decade to fabricate very small nanostructures, with smart stimuli-responsive architectures. It has also demonstrated methods to well decorate surface for enhanced colloidal stability with capabilities to carry both therapy and diagnostic agents. Even satisfactory in vitro and in vivo results have been achieved for most of the research works. Moreover, theranostics depicts great potential to revolutionize modern therapeutics and imaging. Further developments in using such nano-architectures for gene delivery would make the theranostics more personalized and customizable based on individual medical history and genomics. We still have to overcome a lot of obstacles, such as the reproducibility of such complex formulations, which is very difficult with current capabilities. The next hurdle would be to develop such facilities and instruments which would scale up these nanoformulations to higher volumes.

With application of nanomaterials, theranostics approaches depict a more promising medical intervention over conventional treatment strategies. However, the full potential of these materials is yet to be explored. Recently developed green synthesis of nanoparticles is a novel and emerging approach with low capital and operating expenses, in addition to being environmentally benign and enhanced biostability and compatibility. Hence, green synthesis is highly advantageous over traditional chemical and physical methods of nanoparticle synthesis. Theranostics nanovectors face a major challenge of lab-to-industrial-scale translation in terms of manufacture and technology development. This difficulty leads to compromise of stability, structural integrity and shelf life of nanotheranostics formulations. A key factor for maintenance of shelf life of the theranostics formulation is concerned with fragility and reduced activity of the employed targeting agents (i.e. antibodies) during manufacture and use. Nanotheranostics has afforded a novel class of personalized medicine for efficient delivery of therapeutics with reduced off-target toxicity via novel and advanced treatment strategies for individual patients. Moreover, recent advances in designing of multifunctional and modal nanoparticles as delivery technologies serve and promote next-generation molecular and nuclear imaging in clinics for rapid diagnosis and therapy. The blood-brain barrier offers structural and functional complexity, thereby limiting the use of theranostics platforms in clinical translation and personalized treatment of several neurological disorders.

Based on an extensive survey by Grand View Research statistics, the market for nanomedicine is expected to rise up to $ 350 billion worldwide by 2025. A majority of deaths occurring worldwide are associated with cancer metastasis, which is diagnosed late and only revealed upon surgical biopsy. Moreover, some other types of cancer such as lung cancer are more difficult to access for biopsy or require a liquid biopsy-based diagnosis. The liquid biopsy renders information regarding presence of circulating tumour cells (often referred as CTCs). Hence, early detection of cancer with help of nanoscaled diagnostic agents may serve as beneficial breakthrough in medical intervention. Diagnostics play a crucial role in paving road for precise and accurate treatment along with advanced medical interventions for various diseases. Recent reports and published data represent rapid advancement in search of novel biomarkers for disease subtypes, which is further developed by academic researchers and pharmaceutical industries to enhance well-defined and well-designed biomaterials with more individualized treatment strategy, depicting its potential into clinical translation. Modern research displays a paradigm shift in the field of medicine by utilizing integrated, multifunctional, multimodal nanotheranostics. This is rather a steady and slowly progressing field, advancing towards highly efficient personalized medicine along with the companion diagnostic agents at intermediate step. However, more detailed investigation and exploration for use and design of such nanotheranostics are essential.

The question continues to arise over the past few years regarding what will be the future of theranostics. Integrating nanotechnology and next-generation materials won't be enough for

treating severe and deadly diseases. Recently researchers have developed approaches beyond multimodal techniques for next-generation imaging and therapy. An example of such a technique is the 4D-XCAT (four-dimensional extended cardiac-torso) imaging tool. 4D-XCAT is in silico or computer-assisted simulation tool for multiscale and multifunctional modelling of physiological and anatomical features. Techniques such as 4D-XCAT display highly advanced imaging with marked precision and accuracy in imaging therapy (Segars et al. 2018). Furthermore, in assistance to computer simulation for imaging and therapy, in silico designed microscaled multifunctional robots have been fabricated, transcending from conventional to next-generation theranostics. These microbots are specifically designed synthetic or biohybrid constructs for safe, biocompatible therapeutic interventions, aiming towards controlled delivery of bioactives. These miniaturized microbots are highly advanced programmable complex systems, intended for deep cellular access and performing multifunctional molecular diagnostics and therapeutics. Additionally, these micro- and nanomachines possess similar function and physicochemical properties as those of conventional theranostics materials. Moreover, these are highly efficient in performing predefined tasks as well as remote-controlled modulation in preprogrammed function. Depicted as emergent future theranostics, microbots upheld the potential in merging pre-existing drug delivery systems with the next-generation in silico tools. Therefore, it can significantly enhance the drug loading capacity, highly specified targeting and protection against opsonization and more importantly can reduce off-target accumulation as future-generation nanotheranostic systems (Erkoc et al. 2019).

In conclusion, the field of nanotheranostics is rapidly growing and enabling the transition from traditional "trial and error"-based medicine towards a more personalized approach serving as potential and superior clinical outcomes. Nanotheranostics offers a unique and useful tool in classifying, stratifying and selection of patients via prediction of molecular phenotype affirmative response of drug in particular. Nanotheranostics depicts the ability to improve the potency of therapeutic agent, thereby assisting physicians to better understand the highest benefits of particular drugs in individual patients. Moreover, the specific targeting virtues of nanotheranostics will render enhancement in monitoring and maintaining drug safety profile, also reducing off-target toxicity which commonly occurred during traditional chemotherapy. Furthermore, from an economic view, nanotheranostics can lead to cost-effective therapeutic regimes guiding preclinical development or clinical investigation to aid in amplifying the possible research outcomes.

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References

Abedin MR, Umapathi S, Mahendrakar H, Laemthong T, Coleman H, Muchangi D, Santra S, Nath M, Barua S (2018) Polymer coated gold-ferric oxide superparamagnetic nanoparticles for theranostic applications. J Nanobiotechnol 16(1):80

Alibolandi M, Hoseini F, Mohammadi M, Ramezani P, Einafshar E, Taghdisi SM, Ramezani M, Abnous K (2018) Curcumin-entrapped MUC-1 aptamer targeted dendrimer-gold hybrid nanostructure as a theranostic system for colon adenocarcinoma. Int J Pharm 549(1–2):67–75

Bertucci A, Silvestrini S, Corradini R, De Cola L (2018) Loading of PNA and other molecular payloads on inorganic nanostructures for theranostics. In DNA nanotechnology 1811:65–77

Bulte JW, Modo MM (2008) Introduction: the emergence of nanoparticles as imaging platform in biomedicine. In Nanoparticles in biomedical imaging, Springer, New York, NY 102:1–5

Chambre L, Degirmenci A, Sanyal R, Sanyal A (2018) Multi-functional nanogels as theranostic platforms: exploiting reversible and nonreversible linkages for targeting, imaging, and drug delivery. Bioconjug Chem 29(6):1885–1896

Chang CH, Tsai IC, Chiang CJ, Chao YP (2019) A theranostic approach to breast cancer by a quantum dots-and magnetic nanoparticles-conjugated peptide. J Taiwan Inst Chem Eng 97:88–95

Cipreste MF, de Rezende MR, Hneda ML, Peres AM, Cotta AAC, de Carvalho Teixeira V, de Almeida Macedo WA, de Sousa EMB (2018) Functionalized-

radiolabeled hydroxyapatite/tenorite nanoparticles as theranostic agents for osteosarcoma. Ceram Int 44(15):17800–17811

Dai L, Jones CM, Chan WTK, Pham TA, Ling X, Gale EM, Rotile NJ, Tai WCS, Anderson CJ, Caravan P, Law GL (2018) Chiral DOTA chelators as an improved platform for biomedical imaging and therapy applications. Nat Commun 9(1):857

Datta NR, Krishnan S, Speiser DE, Neufeld E, Kuster N, Bodis S, Hofmann H (2016) Magnetic nanoparticle-induced hyperthermia with appropriate payloads: Paul Ehrlich's "magic (nano) bullet" for cancer theranostics? Cancer Treat Rev 50:217–227

Dumortier J, Decullier E, Hilleret MN, Bin-Dorel S, Valette PJ, Boillot O, Partensky C, Letoublon C, Ducerf C, Leroy V, Vuillez JP (2014) Adjuvant intraarterial lipiodol or 131I-lipiodol after curative treatment of hepatocellular carcinoma: a prospective randomized trial. J Nucl Med 55(6):877–883

Efremova MV, Naumenko VA, Spasova M, Garanina AS, Abakumov MA, Blokhina AD, Melnikov PA, Prelovskaya AO, Heidelmann M, Li ZA, Ma Z (2018) Magnetite-gold nanohybrids as ideal all-in-one platforms for theranostics. Sci Rep 8(1):11295

Emi T, Michaud K, Orton E, Santilli G, Linh C, O'Connell M, Issa F, Kennedy S (2019) Ultrasonic generation of pulsatile and sequential therapeutic delivery profiles from calcium-crosslinked alginate hydrogels. Molecules 24(6):1048

Engberink RDO, Van Der Pol SM, Walczak P, Van Der Toorn A, Viergever MA, Dijkstra CD, Bulte JW, De Vries HE, Blezer EL (2010) Magnetic resonance imaging of monocytes labeled with ultrasmall superparamagnetic particles of iron oxide using magnetoelectroporation in an animal model of multiple sclerosis. Mol Imaging 9(5):7290–2010

Erkoc P, Yasa I, Ceylan H, Yasa O, Alapan Y, Metin Sitti M (2019) Mobile microrobots for active therapeutic delivery. Adv Ther 2(1):1800064

Evangelopoulos M, Parodi A, Martinez J, Tasciotti E (2018) Trends towards biomimicry in theranostics. Nanomaterials 8(9):637

Fernandes RS, Silva JO, Mussi SV, Lopes SC, Leite EA, Cassali GD, Cardoso VN, Townsend DM, Colletti PM, Ferreira LA, Rubello D (2018) Nanostructured lipid carrier co-loaded with doxorubicin and docosahexaenoic acid as a theranostic agent: evaluation of biodistribution and antitumor activity in experimental model. Mol Imaging Biol 20(3): 437–447

Fiegel V, Harlepp S, Begin-Colin S, Begin D, Mertz D (2018) Design of protein-coated carbon nanotubes loaded with hydrophobic drugs through sacrificial templating of mesoporous silica shells. Chem Eur J 24(18):4662–4670

Gallicchio R, Nardelli A, Mainenti P, Nappi A, Capacchione D, Simeon V, Sirignano C, Abbruzzi F, Barbato F, Landriscina M, Storto G (2016) Therapeutic strategies in HCC: radiation modalities. Biomed Res Int 2016:1295329

Gholami L, Tafaghodi M, Abbasi B, Daroudi M, Kazemi Oskuee R (2019) Preparation of superparamagnetic iron oxide/doxorubicin loaded chitosan nanoparticles as a promising glioblastoma theranostic tool. J Cell Physiol 234(2):1547–1559

Goldsmith SJ (2010) Radioimmunotherapy of lymphoma: Bexxar and Zevalin. In Seminars in nuclear medicine, WB Saunders 40(2):122–135

González-Prieto C, Lesser CF (2018) Rationale redesign of type III secretion systems: toward the development of non-pathogenic E. coli for in vivo delivery of therapeutic payloads. Curr Opin Microbiol 41:1–7

Gyawali D, Kim JP, Yang J (2018) Highly photostable nanogels for fluorescence-based theranostics. Bioactive Mater 3(1):39–47

He K, Ran H, Su Z, Wang Z, Li M, Hao L (2019) Perfluorohexane-encapsulated fullerene nanospheres for dual-modality US/CT imaging and synergistic high-intensity focused ultrasound ablation. Int J Nanomedicine 14:519

Hong G, Antaris AL, Dai H (2017) Near-infrared fluorophores for biomedical imaging. Nature Biomed Eng 1(1):0010

Hu P, Wu T, Fan W, Chen L, Liu Y, Ni D, Bu W, Shi J (2017) Near infrared-assisted Fenton reaction for tumor-specific and mitochondrial DNA-targeted photochemotherapy. Biomaterials 141:86–95

Huang H, Dong Y, Zhang Y, Ru D, Wu Z, Zhang J, Shen M, Duan Y, Sun Y (2019) GSH-sensitive Pt (IV) prodrug-loaded phase-transitional nanoparticles with a hybrid lipid-polymer shell for precise theranostics against ovarian cancer. Theranostics 9(4):1047

Idée JM, Louguet S, Ballet S, Corot C (2013) Theranostics and contrast-agents for medical imaging: a pharmaceutical company viewpoint. Quant Imaging Med Surg 3(6):292

Jędrzak A, Grześkowiak BF, Coy E, Wojnarowicz J, Szutkowski K, Jurga S, Jesionowski T, Mrówczyński R (2019) Dendrimer based theranostic nanostructures for combined chemo-and photothermal therapy of liver cancer cells in vitro. Colloids Surf B: Biointerfaces 173:698–708

Jin G, He R, Liu Q, Lin M, Dong Y, Li K, Tang BZ, Liu B, Xu F (2019) Near-infrared light-regulated cancer theranostic nanoplatform based on aggregation-induced emission luminogen encapsulated upconversion nanoparticles. Theranostics 9(1):246

Kumeria T, McInnes SJ, Maher S, Santos A (2017) Porous silicon for drug delivery applications and theranostics: recent advances, critical review and perspectives. Expert Opin Drug Deliv 14(12):1407–1422

Liu Y, Liu Y, Bu W, Xiao Q, Sun Y, Zhao K, Fan W, Liu J, Shi J (2015) Radiation−/hypoxia-induced solid tumor metastasis and regrowth inhibited by hypoxia-specific upconversion nanoradiosensitizer. Biomaterials 49:1–8

Liu Y, Nie L, Chen X (2016) Photoacoustic molecular imaging: from multiscale biomedical applications towards early-stage theranostics. Trends Biotechnol 34(5):420–433

Liu R, Xiao W, Hu C, Xie R, Gao H (2018) Theranostic size-reducible and no donor conjugated gold nano-

cluster fabricated hyaluronic acid nanoparticle with optimal size for combinational treatment of breast cancer and lung metastasis. J Control Release 278:127–139

Marchetti C, Palaia I, Giorgini M, De Medici C, Iadarola R, Vertechy L, Domenici L, Di Donato V, Tomao F, Muzii L, Panici PB (2014) Targeted drug delivery via folate receptors in recurrent ovarian cancer: a review. Onco Targets Ther 7:1223

Matteson EL, Lowe VJ, Prendergast FG, Crowson CS, Moder KG, Morgenstern DE, Messmann RA, Low PS (2009) Assessment of disease activity in rheumatoid arthritis using a novel folate targeted radiopharmaceutical Folatescan™. Clin Exp Rheumatol 27(2):253

Miller ML, Shizuka M, Wilhelm A, Salomon P, Reid EE, Lanieri L, Sikka S, Maloney EK, Harvey L, Qiu Q, Archer KE (2018) A DNA-interacting payload designed to eliminate cross-linking improves the therapeutic index of antibody–drug conjugates (ADCs). Mol Cancer Ther 17(3):650–660

Misra C, Yadav AB, Verma RK (2018) Carbon-based nanofibers: fullerenes, diamond, and carbon nanostructures. In: Barhoum A, Bechelany M, Makhlouf A (eds) Handbook of nanofibers. Springer, Cham, pp 1–14

Nagel G, Tschiche HR, Wedepohl S, Calderón M (2018) Modular approach for theranostic polymer conjugates with activatable fluorescence: impact of linker design on the stimuli-induced release of doxorubicin. J Control Release 285:200–211

Näkki S, Martinez JO, Evangelopoulos M, Xu W, Lehto VP, Tasciotti E (2017) Chlorin e6 functionalized theranostic multistage nanovectors transported by stem cells for effective photodynamic therapy. ACS Appl Mater Interfaces 9(28):23441–23449

Naveed F, Fisher R, Engel JS, Lu J, Low P, Amato RJ (2004) Folate-scan in subjects with suspected metastatic renal cell carcinoma. J Clin Oncol 22(14):4751–4751

Neuwelt EA, Hamilton BE, Varallyay CG, Rooney WR, Edelman RD, Jacobs PM, Watnick SG (2009) Ultrasmall superparamagnetic iron oxides (USPIOs): a future alternative magnetic resonance (MR) contrast agent for patients at risk for nephrogenic systemic fibrosis (NSF)? Kidney Int 75(5):465–474

Ortega-Liebana MC, Encabo-Berzosa MM, Casanova A, Pereboom MD, Alda O, Hueso JL, Santamaria J (2019) Upconverting carbon nanodots from EDTA as near-infrared activated phototheranostic agents. Chem Eur J 25(21):5539–5546

Reimer P, Balzer T (2003) Ferucarbotran (Resovist): a new clinically approved RES-specific contrast agent for contrast-enhanced MRI of the liver: properties, clinical development, and applications. Eur Radiol 13(6):1266–1276

Rong P, Huang P, Liu Z, Lin J, Jin A, Ma Y, Niu G, Yu L, Zeng W, Wang W, Chen X (2015) Protein-based photothermal theranostics for imaging-guided cancer therapy. Nanoscale 7(39):16330–16336

Sakr TM, Khowessah OM, Motaleb MA, El-Bary AA, El-Kolaly MT, Swidan MM (2018) I-131 doping of silver nanoparticles platform for tumor theranosis guided drug delivery. Eur J Pharm Sci 122:239–245

Segars W Paul et al (2018) Application of the 4-D XCAT Phantoms in Biomedical Imaging and Beyond. IEEE Transactions on Medical Imaging 37(3): 680–92

Shen MY, Liu TI, Yu TW, Kv R, Chiang WH, Tsai YC, Chen HH, Lin SC, Chiu HC (2019) Hierarchically targetable polysaccharide-coated solid lipid nanoparticles as an oral chemo/thermotherapy delivery system for local treatment of colon cancer. Biomaterials 197:86–100

Shervedani RK, Foroushani MS, Kefayat A, Torabi M, Rahsepar FR (2018) Construction and characterization of a theranostic system based on graphene/manganese chelate. Biosens Bioelectron 117:794–801

Su G, Miao D, Yu Y, Zhou M, Jiao P, Cao X, Yan B, Zhu H (2019) Mesoporous silica-coated gold nanostars with drug payload for combined chemo-photothermal cancer therapy. J Drug Target 27(2):201–210

Upponi JR, Jerajani K, Nagesha DK, Kulkarni P, Sridhar S, Ferris C, Torchilin VP (2018) Polymeric micelles: Theranostic co-delivery system for poorly water-soluble drugs and contrast agents. Biomaterials 170:26–36

Usman M, Hussein M, Kura A, Fakurazi S, Masarudin M, Ahmad Saad F (2018) Graphene oxide as a nanocarrier for a theranostics delivery system of protocatechuic acid and gadolinium/gold nanoparticles. Molecules 23(2):500

Victor SP, Paul W, Sharma CP (2018) Calcium phosphate nanoplatforms for drug delivery and theranostic applications. In: Drug delivery nanosystems for biomedical applications. Sharma CP, Elsevier, pp 163–179

Wang C, Xue R, Gulzar A, Kuang Y, Shao H, Gai S, Yang D, He F, Yang P (2019) Targeted and imaging-guided chemo-photothermal ablation achieved by combining upconversion nanoparticles and protein-capped gold nanodots. Chem Eng J 370:1239–1250

Weiner RE, Thakur ML (2005) Radiolabeled peptides in oncology. BioDrugs 19(3):145–163

Wu Z, de Ávila BEF, Martín A, Christianson C, Gao W, Thamphiwatana SK, Escarpa A, He Q, Zhang L, Wang J (2015) RBC micromotors carrying multiple cargos towards potential theranostic applications. Nanoscale 7(32):13680–13686

Wyszogrodzka G, Dorożyński P, Gil B, Roth WJ, Strzempek M, Marszałek B, Węglarz WP, Menaszek E, Strzempek W, Kulinowski P (2018) Iron-based metal-organic frameworks as a Theranostic carrier for local tuberculosis therapy. Pharm Res 35(7):144

You, Chaoqun, et al. (2018) Near Infrared Radiated Stimulus-Responsive Liposomes Based on Photothermal Conversion as Drug Carriers for Co-Delivery of CJM126 and Cisplatin. Materials Science and Engineering C 80: 362–70

Zhang K, Zhang Y, Meng X, Lu H, Chang H, Dong H, Zhang X (2018) Light-triggered theranostic liposomes for tumor diagnosis and combined photodynamic and hypoxia-activated prodrug therapy. Biomaterials 185:301–309