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REVIEW ARTICLE

CANCER NANOTHERANOSTICS: A NEW PARADIGM OF SIMULTANEOUS DIAGNOSIS AND THERAPY

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ABSTRACT

Despite improvements in our understanding of cancer and the emerging concept of personalized medicine for the treatment of this disease, it is still one of the leading causes of death worldwide. Although, in recent years, significant advances have been achieved in cancer therapy, many tumors are still challenging to treat and novel strategies are required to effectively combat this deadly disease. Nanotheranostics is a burgeoning field which makes use of nanotechnology for diagnosis and therapy of cancer. The recent advancement in the area of nanotechnology has enabled a new generation of different types of nanomaterials composed of either inorganic or polymer based nanoparticles to be useful for nanotheranostics applications such as to diagnose and treat diseases and monitoring the therapeutic response in vivo at molecular level; to enhance the control, evaluation and optimization of drug delivery and release; to target the drug by conjugating theranostic nanoplatformes with biological ligands. This review, therefore, summarizes the various nanocarriers developed so far for the simultaneous imaging and therapy, strategies for their targeted delivery, their potential applications and the challenges in their development and application for cancer therapy.

Key words: Cancer; Cancer therapy; Nanoparticles; Nanotheranostics.

1. INTRODUCTION

Cancer is a multi-factorial disease primarily characterized by uncontrolled proliferation of cells, local tissue invasion and their ability to metastasize. It remains the third leading cause of death in the world after heart and infectious diseases [1].

Years of intense research and billions of dollars in spending have dramatically increased knowledge of the causes and biology of cancer, leading to the development of many improved treatment strategies. Yet, the diagnosis and treatment of many cancers still remain elusive and a major barrier to effective clinical outcomes, thereby, millions of deaths every year are still caused by cancer. Thus, early detection and development of even more effective therapies are crucial for the optimal management of cancer [2].

Current cancer treatment relies on the use of surgery, radiotherapy and chemotherapy from which chemotherapy is the common approach to the chronic management of cancer. However, in the majority of cases, surgery and radiotherapy are used in combination with chemotherapy [3]. Unfortunately, current cancer therapies are largely limited by inability to bypass biological barriers, nonspecific delivery and poor biodistribution of drugs, ineffectiveness against metastatic disease, drug resistance of cancers, and lack of an effective modality for treatment monitoring [4].

Over the past two decades, nanotechnology-based approaches have emerged as an exciting field of cancer therapy with promises to overcome these challenges by enabling the engineered nanomedicines to navigate the body in very specific ways, i.e., nanotechnology facilitates controlled, tumor specific drug accumulation and release [5].

Flurries of developments in nanoscience and biomedicine and the convergence of these disciplines have now expanded the ability to design and construct "multifunctional" nanoparticles, combining targeted therapeutic and diagnostic functions in a same entity [6]. Therefore, theranostic nanomedicines emerge as an alternative to the separate administration of diagnostic probes and pharmacologically active molecules. The word "theranostics" refers to the simultaneous integration of diagnosis and therapy [7].

The vision for nanotheranostics is to design nanocarriers which will serve a dual purpose by allowing both treatment and diagnosis to be contained in an 'all in one' package.

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In fact, the nanocarriers will be designed to target a certain disease. A probe inserted into their design allows them to be tracked in the body and a drug that is carried together with the probe will be released if the nanocarrier binds to the cell, starting the therapy of the disease, making the treatment of the diagnosis immediate and saving valuable time [8]. Hence, in this review, the various nanocarriers developed so far for the simultaneous imaging and therapy, the formulation and strategies by which these nanotheranostics are delivered to the target site, the application of nanotheranostics and challenges in using nanotheranostics for cancer therapy are discussed.

2. NANOTHERANOSTIC AGENTS FOR CANCER IMAGING

Different types of nanomaterials have been developed to provide contrast in medical imaging. They can be constructed by either organic materials (liposomes, polymeric micelles, dendrimers, etc), inorganic ones (iron oxide, gold, mesoporous silica, etc), or organic inorganic hybrid materials [9]. Nanotheranostics can be classified based on the nanoplatform delivery system employed or by the agents coupled with drugs to provide imaging functions. An overview of the different types of nanotheranostics is discussed below with their schematic diagram (Figure 1)

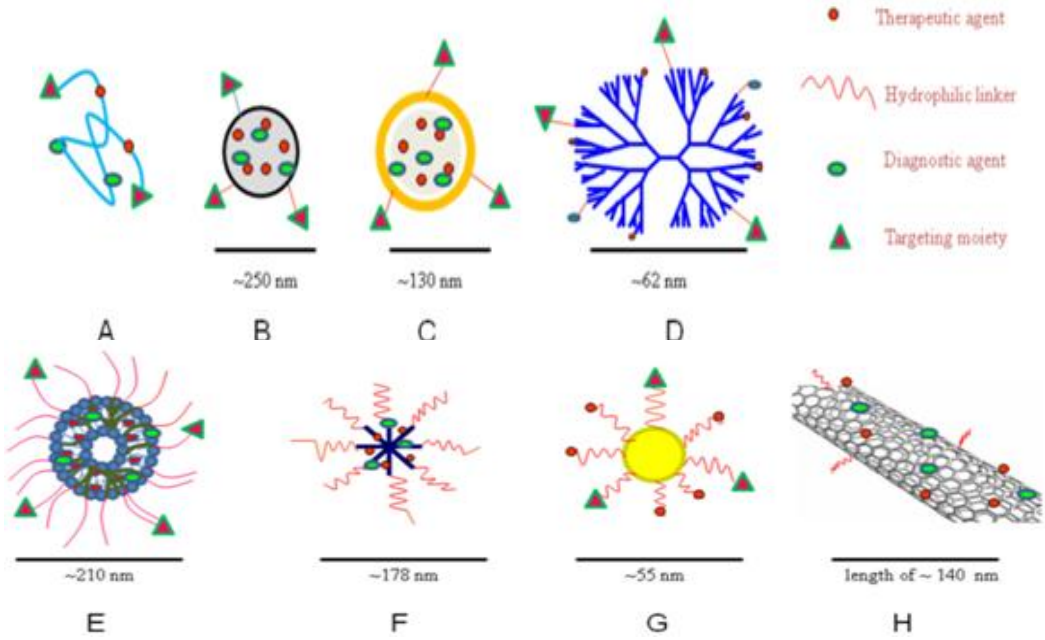

Figure 1: Schematic diagram of theranostics: A) polymer-drug conjugate; B) polymeric nanoparticle; C) solid lipid nanoparticle; D) dendrimer; E) liposome; F) micelle; G) gold nanoparticle; and H) carbon nanotube [9].

2.1. Liposome and micelle based theranostics

Liposomes and micelles are by far the most widely used and studied nanomaterials for cancer therapy. These lipid-based nanoparticles (LNPs) are synthesized from lipids containing a hydrophilic head group and lipophilic tail that spontaneously form spheres at critical concentrations [10, 11]. Liposomes are spherical vesicles with concentric phospholipid bilayers enclosing aqueous compartment [12] whereas micelles or polymeric micelles are nanosized (typically in the range of 20–100 nm) spherical structures, composed of amphiphilic block copolymers, which self-assembles to form a core/shell structure in aqueous media [13].

Currently theranostic liposomes are either being designed bearing non-invasive multimodal imaging agents like fluorescent probes, radio-isotopes and nanoparticle like magnetic nanoparicles or quantum dots (QDs). Diagnosis by theranostic liposomes have been reportedly done by utilizing magnetic resonance imaging (MRI), positron emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) and near infrared resonance (NIR) fluorescent imaging [14].

The imaging agents can be entrapped within the hydrophobic core or linked covalently to the surface of the liposomes and the therapeutic agent can be either encapsulated in the lipophilic core or embedded in the lipophilic bilayer shell. The liposomes can then be further conjugated with molecular probe for targeting. Such multi-functional liposomes may circulate for prolonged periods in the blood, evading host defenses, and gradually release drug by targeting and simultaneously facilitate *in vitro* or *in vivo* imaging [7]. For instance, Shihong Li and his co-workers synthesized liposomal nanotheranostic of doxorubicin by preparing Gadolinium-based liposomes composed and found a promising result [15].

Similarly, micelles are emerging as powerful, multifunctional nanotherapeutic platforms for cancer imaging and therapeutic applications and as theranostic delivery systems in cancer management [11]. Sailor and park [16] have established a multifunctional micellar platform that incorporates a targeting ligand, pH-

stimulated release of doxorubicin (DOX), and an MRI-visible agent. In this design, DOX and a cluster of superparamagnetic iron oxide nanoparticles (SPIO) nanoparticles (8 nm in diameter) were loaded into the cores of polyethyleneglycol-polylacticacid (PEG-PLA) micelles, while a cRGD ligand on the micelle surface (cRGD-DOX-SPIO micelles) was used for targeting. The resulting targeted, multifunctional micelles, measuring 45-48 nm in diameter, showed increased uptake *in vitro* in a_Vb_3-over expressing endothelial tumor cells.

2.2. Polymer and dendrimer based theranostics

Polymeric nanomaterials have been extensively studied for their biocompatibility, versatility and multi-functionality and offer a suitable platform for tumor imaging and therapy because of their well-defined and controllable physiochemical properties, size, and degradation rate, their surface "upgradability" (meaning their surfaces can be easily modified with various targeting ligands) and their ability to carry various types of therapeutic agents and/or imaging probes (Figure 2) [17]. So far, a number of polymeric platforms have been applied in cancer therapy to enhance anticancer agents' efficacy, prolong drug circulation half-life, and provide stimuli-responsive drug release and targeting delivery. Some of these polymer-based nanocarriers are currently under various stages of clinical development [18].

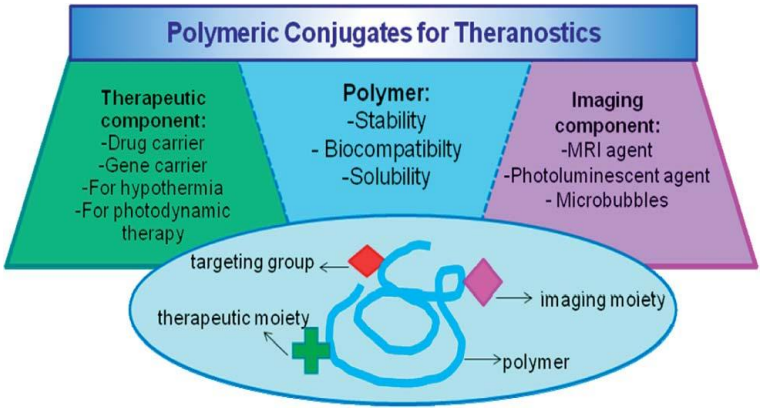

Figure 2: The three main components that a polymer conjugate combines for theranostics[18]

Sailor and Park [16] has synthesized multifunctional polymer system co-encapsulated with a hydrophobic therapeutic agent (doxorubicin) and either hydrophobic superparamagnetic nanocrystals or hydrophobic quantum dots, using an oil-in-water emulsion and a subsequent solvent evaporation technique and a folate group was coupled onto the surface of the polymeric hybrid nanoparticles to target cancer cells' folate receptor. The prepared polymeric hybrid nanoparticles had uniform shapes and well targeted as it was evidenced by optical (quantum dots) and MR (magnetic nanocrystals) imaging techniques [1]. In another study done by loading poly (HPMA) based theranostic copolymers with Cu-64 which acts as intrinsic theranostic agent and cRGD as targeting ligand for targeting tumor angiogenesis, The PET showed higher accumulation of Poly(HPMA)-c(RGD)-^{64}Cu in tumor sites after IV injection than the non targeted Poly(HPMA)-^{64}Cu conjugate [19].

Like polymer nano particles, dendrimer-based NPs have also been employed as nanotheranostic agents because of their unique characteristics which a single dendrimer can act as a platform for imaging and targeting agents to identify cancer cells [20, 21]. Taking these unique characteristics as an advantage different studies has been done [22, 23]. Among these, Zhang and his group [22] have synthesized an ethylenediamine core poly (amido amine) (PAMAM) generation five dendrimer which has a diameter of about 5 nm and more than 100 functional primary amines on the surface that has the potential to be used for targeting, imaging, and intracellular drug delivery, by covalently attaching to folic acid, fluorescein, and methotrexate in proper ratio. This multifaceted theranostic preparation, showed 100-fold higher cytotoxicity than free methotrexate.

2.3. Noble metal based theranostics

Noble metals like gold, silver, and/or platinum have been extensively studied as theranostics due to their unique and distinctive characteristics such as high surface-to-volume ratio, broad optical properties, ease of synthesis, and facile surface chemistry and functionalization [24]. Noble metal NPs present optical properties, which can be easily tuned to desirable wavelengths according to their shape, and composition enabling their imaging and photothermal applications under native tissue. These NPs can also be easily functionalized with various moieties, such as antibodies, peptides, and/or DNA/RNA to specifically target different cells and with biocompatible polymers. Moreover, they can efficiently convert light or radio frequencies into heat, thus enabling thermal ablation of targeted cancer cells [25].

2.3.1. Gold-based theranostics

Due to their potential to facilitate both the diagnosis and treatment of cancer through their advantageous chemical and physical properties like superior biocompatibility and well-established strategies for surface modification (i.e. gold-thiol bonding), gold-based nanomaterials have been investigated as theranostic nanoplatforms [26]. One of the most attractive attributes of gold nanomaterials (GNMs) is the tunable optical property that mediates the

localized surface plasmon resonance (LSPR). The LSPR of gold nanomaterials can be adjusted by tuning their morphology; gold (Au) NP, nanorod (AuNR), nanoshell, and nanocage exhibit distinctive optical and thermal properties, which can readily upgrade gold nanomaterials to be prospective theranostic agents [27]. Wang and his coworkers [9] have developed leyered double hydroxide-gadolinium/gold (LDH-Gd/Au) nanocomposite platform for CT/MRI dual-modality imaging and anti-cancer drug delivery. The LDH-Gd/Au nanocomposite showed high non-anionic anti-cancer drug DOX loading capacity (264 mg drug/g carrier), and the loaded DOX shows an interesting pH-responsive release feature, which is favorable for avoiding quick drug release in the neutral blood system but promoting drug release at acidic tumor sites or within cells. Despite their property is fascinating to tune as theranostics, GNMs have their own intrinsic disadvantages like high cost of production and an issue of stability in physiological conditions. For clinical translation of GNMs, more stable surface chemistry is greatly required.

2.3.2. Silver based theranostics

The cytotoxicity of silver nanoparticles (Ag NPs) to various cell lines is effectuated by conjugating with various chemicals, biomolecules, and anticancer drugs via covalent or non-covalent bonds. For instance, Mukherjee and his coworker [29] have developed bio-synthesized silver based nanoparticles (b-AgNps) from reduction of silver nitrate (AgNO3). The formed nanoparticle exhibited multifunctional characteristics for targeted drug delivery and fluorescence imaging of cells that could be utilized to detect the localization of drug molecules inside the cancer. Thus, there is a strong hope in b-AgNps for their use as theranostic agents in cancer diagnosis and therapy [28]. However, the only limitation that withholds Ag Nps from extensive application in cancer therapy and diagnosis is its poor biocompatibility to the *in vivo* system. One recent works in this regard suggested that the aforementioned problem can be overcome by capping Ag Nps with stem latex from a medicinal plant, *Euphorbia nivulia*. The modified NPs are found to be biocompatible and cytotoxic against human lung carcinoma cells (A549) in a dose-dependent manner [17].

2.4. Quantum dots (QDs) or Semiconductor based theranostics

Quantum dots (QDs), which are small 2-10 nm light-emitting nanocrystals made from semiconductor materials typically from selenides or sulfides of cadmium or zinc, are becoming an important class of biomaterials, because they possess unique optical and electronic properties depending on their size and composition. To improve QD solubility, sensitivity, specificity, and visualization in the target tissue, the surface of QD can be modified by ligand exchange with simple thiol-containing molecules, dendrons, peptides, and encapsulation by a layer of amphiphilic copolymers. This strategy not only helps to facilitate solubilization, but also provides a linker for bioconjugation of peptides, antibodies, oligonucleotides, or small molecule drugs, thereby multi-functionalizing the QDs for tumor targeting, tumor imaging and drug delivery [29].

QD based theranostic agents can be prepared by loading QDs via physical adsorption such as methotrexate (MTX) loaded QDs or co-encapsulation of QDs and drug into lipid micelles [30]. Following the above method of preparation Liu *et al* have successfully prepared multi-functional QD in which a targeting ligand (RNA aptamers covalently attached to the surface of QD, which also serve as a drug carrier vehicle) and doxorubicin are incorporated as a therapeutic agent and a drug, respectively [31].

2.5. Carbon nanotubes and fullerenes

Carbon nanotubes (CNTs) are cylindrical tubes composed solely of carbon and can either be formed as single-walled (consists of a single graphene cylinder) with a diameter of 0.8 - 2 nm or multi-walled (comprises several concentric graphene cylinders) with a diameter of 5-20 nm. Different nanocarbons such as carbon nanotubes, graphene, fullerene, nanodiamond and carbon nanoparticles (CNPs) (Figure 3) have been developed as delivery vehicles for imaging and therapeutic agents [32].

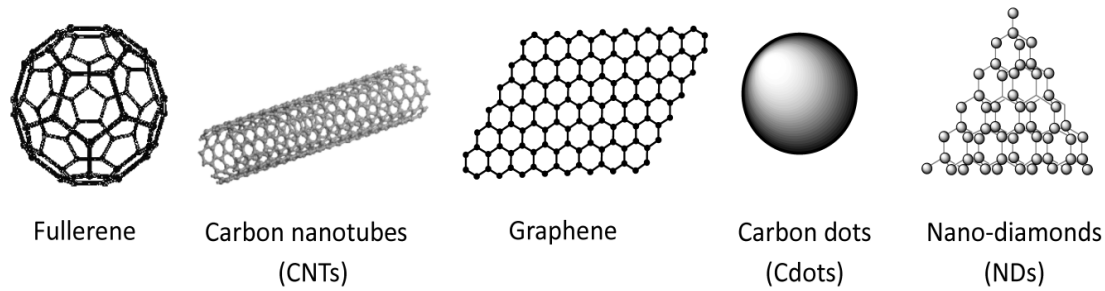

Figure 3: Different types of nano-carbons explored for theranostic applications [32].

Their interesting physico-chemical features such as high surface area, ultra-light weight, pseudoaromatic structure, tunable surface chemistry, ease of drug loading, fluorescence detectability and photoacoustic effects make them a potential asset in the arsenal of theranostic nanocarriers. Recent expansion of surface engineering and bioconjugation techniques has accelerated the growth of multi-functional CNT-based platforms, concomitantly combined with multiple diagnostic and therapeutic entities. Such multifunctional yet 'chemically partitioned' CNTs can easily penetrate biological barriers like a 'nanoneedle' facilitating the internalization of various cargos inside the cells that would not otherwise be taken up [5]. A promising result

has been found in a study done by encapsulating Doxorubicin as chemotherapeutic agent and gadolinium-based contrast agents for MRI imaging within the lipid bilayer of fullerene liposomes to target interleukin (IL-13) receptors in brain cancer therapy. After verifying the selective binding of fullerene liposome based theranostics to the IL-13 receptor, its antitumor effect was tested in mice bearing brain tumors and better shrinkage of the tumor was observed [33].

2.6. Magnetic nanoparticles based theranostics

Magnetic NP-based theranostics, along with their magnetic property as nanostructured contrast probes for MRI, are beneficial due to their biocompatibility, cost-effectiveness and their large surface area to volume ratio that enables loading of a wide range of functionalities, such as targeting, imaging and therapeutic features, onto their surfaces. Among the magnetic NPs, superparamagnetic iron oxide nanoparticles (SPIONPs), mainly magnetite and maghemite, are the most commonly used nanomaterials [34].

The main drawback of magnetic nanparticles is their poor water solubility and intracellular aggregation. In order to confer colloidal suspendability to the particles, hydrophilic polymers are added to passivate the nanocrystal surface that would typically protect particles from aggregation. For instance, Santra and his coworkers utilized poly (acryl amide) (PAA) to coencapsulate a lipophilic NIR dye and the anticancer drug taxol within hydrophobic pockets, resulting in a theranostic nanocarrier for dual fluorescence and MR-based imaging and monitoring of drug delivery. Foliate; furthermore, was conjugated onto PAA-IONPs, yielding targeting functionality aimed at the targeted killing of foliate receptor-overexpressing cancer cells, demonstrated by optical/MR imaging. In addition, their work pointed out that incorporating polymer could somehow alleviate the poor water solubility problem of magnetic nanoparticles [35].

2.7. Silica based nanotheranostics

The properties of many nanomaterials are dependent on their size as it approaches the nanosize range and the percentage of atoms present on their surfaces, but silica-based nanoparticles (SiNPs) have constant physical properties similar to those of bulk materials, except that the total surface area increases as the size decreases. Indeed, what really makes SiO2 NPs predominate in nanobiomedicine is the higher surface area, their well-defined tunable nanostructures and well-established siloxane chemistry, which allow successful fabrication of the desired surface for diagnostic and therapeutic requests [26]. There are two types of silica nanoparticles, solid silica nanoparticles and mesoporous silica nanoparticles. Methods such as sol-gel synthesis and microemulsion have been employed to prepare silica based nanoparticles for diagnostic imaging and therapeutic applications [36]. A wide variety of imaging, targeting ligands and therapeutic agents, such as superparamagnetic iron oxide nanoparticles, and Gd complexes for MRI imaging, quantum dots, genes, chemotherapeutic drugs like Doxorubicin, Captothecin, Paclitaxel, have been loaded/grafted/encapsulated into mesoporous silica based nanotheranosticss which are expected to satisfy the clinical requirements following the systematic investigation of their biological effects and bio-safety, and finally find their applications in clinical practices to benefit human beings [37]. Chen and his coworker [5] reported development of trifunctionalized MSNs for theranostic application that combined imaging, targeting, and therapeutic agent in one single-particle platform. This theranostic platform exhibited excellent targeting of human glioblastoma cells and minimal collateral damage, but highly potent therapeutic effects.

3. TRIGGERED NANOTHERANOSTIC DELIVERY

Obviously, both passive and active targeting mechanisms can be used to target nanotheranostics to specific cancerous cell. In addition to passive accumulation and active tumor-specific targeting strategies, another important approach for tumor-localized drug release is to design ‘smart’ nanotheranostics, which, can respond to an extrinsic stimulus (*e.g.* Temperature, magnetic field, ultrasound, and light) or an intrinsic trigger (*e.g.* pH, glucose, redox potential, and lysosomal enzymes) which is specific to the disease environment [38].

3.1. Temperature responsive nanotheranostics

Temperature responsive liposomal (TSL) formulations hold great promise to further increase the drug concentration and its bioavailability in the tumor. However, the need for monitoring the drug release process has led to the development of MRI encapsulated TSLs, which allows drug delivery under imaging guidance. When drug and a contrast agent (CA) release occurs simultaneously, the observed MRI contrast change can be used for quantification of the drug release [39]. TSLs release drugs encapsulated in the liposome lumen at the melting phase transition temperature (T_m) of the bilayer. At T_m, the lipid membrane undergoes a gel to a liquid-crystalline phase transition because of structural changes in the liposomal membrane. This is accompanied by transient membrane defects, which facilitate the rapid release of liposomal contents [40].

3.2. PH responsive nanotheranostics

The pH of cancer cells is lower than that of normal cells as a result of increased lactic acid production. The acid is also released to extracellular regions lowering the pH to bellow 7.4. This characteristic of cancer cells allows for pH responsive nanocarriers containing both imaging and therapeutic agents to specifically deliver into cancer cells and release their contents. LDH-Gd/Au nanocomposite platform has synthesized for CT/MRI dual-modality imaging and anti-cancer drug delivery. The LDH-Gd/Au nanocomposite shows high non-anionic anti-cancer drug DOX loading capacity (264 mg drug/g carrier), and the loaded DOX shows an interesting pH-responsive release feature, which is favorable for avoiding quick drug release in the neutral blood system but promoting drug release at acidic tumor sites or within cells [9].

3.3. Magnetic field responsive nanotheranostics

Magnetic nanoparticles have the capability to produce heat under externally applied magnetic field. While the

term "Hyperthermia" in the literature, so far has been confined only to include the use of heat for therapy, it was found from the recent literature studies that MNP-based hyperthermia could also be utilized to generate intense local heating within polymeric matrices thereby creating voids for the release of encapsulated drugs. One example of an activable drug-delivery system by a magnetic field used dextran-coated IONPs with MRI capability and conjugated fluorescein-labeled 18 base-pair oligonucleotide duplexes to the particle. Upon electromagnetic field activation, the duplex structure of the fluorescein-labeled oligonucleotides melted and released the fluorescein, which served as the model drug, into the tumor model [41].

4. APPLICATIONS OF NANOTHERANOSTICS IN CANCER THERAPY

Before initiating treatment of various diseases, primarily cancer, it is essential to carry out diagnostic imaging to understand the cellular phenotype(s) and heterogeneity of the tumor. The ultimate goal of the theranostic field is to gain the ability to image and monitor the diseased tissue, delivery kinetics, and drug efficacy. Here below the applications of nanotheranostics in the treatment of various types of cancers are presented.

4.1. Solid Tumors

A solid tumor consists of an abnormal mass of cells which may stem from different tissue types such as liver, colon, breast, or lung, and which initially grows in the organ of its cellular origin. When these tumors reach a critical size, diffusion of chemotherapeutic agents into the tumor becomes impaired. Thus new strategies that overcome this problem should be designed. Owing to their small size, nanotheranostics, especially those conjugated with targeting ligands have the ability to deliver the therapeutic agent deep into the tumor tissue thereby enhancing the accumulation of drugs within the tumor. Imaging agents encapsulated with the chemotherapeutic agents will provide real time visualization of target as well as off target site accumulation of chemotherapeutic agents helping immediate assessment of over/under treatment conditions [42].

4.2. Metastases

Metastasis is the development of secondary malignant growths at distant sites as a result of the spread of cancer from a primary tumor site. It occurs through the process of spreading cancers into neighboring normal tissues, intravasation in to the blood stream or lymphatic's, extravasation from the blood stream into different tissues of the body and the formation of a metastasized tumor. Metastases primarily develop during the late stages of cancer and accounts for greater than 90% of all cancer related deaths [43]. Various treatment strategies have been designed for the treatment of metastasized cancers, but due to the complexity of tumor progression, tumor composition, and drug resistance mechanisms these are unable to improve the prognosis apart from improving survival. Thus nanotheranostics are believed to overcome this problem by early detection of tumors and inhibiting cell invasion by the interaction of specifically engineered nanomaterials with cell surface proteins involved in cell invasion. They also enable the researchers to visualize and analyze the distribution of drugs to all metastasized cancer cells and to monitor treatment efficacy [44].

4.3. Multidrug resistance

Drug resistance, which allows tumors to evade chemotherapeutic agents, has emerged as a major obstacle that limits the efficacy of chemotherapy [45]. This mechanism for tumor survival under chemotherapeutic treatment is known as multidrug resistance (MDR). P-glycoprotein (P-gp), an efflux transporter, which is overexpressed on the plasma membrane of cancer cells, is thought to be responsible for MDR [46].

Different mechanisms can be employed for uptake of theranostic nanomedicines into the tumor. Irrespective of the exact mode of cellular entry, endocytosed nanomedicines eventually end up in lysosomes, and thus are carried relatively deep into cells, far beyond the reach of trans-membrane localized drug efflux pumps. In theory, this strategy, therefore ensures efficient delivery of chemotherapeutic agents into the cytoplasm of cells, without being sensed and removed by MDR proteins as opposed to free (i.e. non-nanomedicine-associated) chemotherapeutic drugs, which upon passive diffusion across the cellular membrane are rapidly sensed and effluxed by MDR proteins [47].

4.4. Hematological cancers

Hematologic cancer is a cancer that affects the body's blood, bone marrow or lymphatic system. As compared to solid tumors, these cancers inflict greatest challenge for therapy. The tumor microenvironment of these cancers is extremely diverse than with solid tumors and offers growth factors for cancer cells growth and survival resulting in *de novo* drug resistance. Likewise, treated cancer cells can lyse and release their components directly into the blood, which leads to potentially lethal electrolyte and metabolic disturbances. Therefore, theranostic nanoparticles aim to induce apoptosis through the formation of free radicals, so that cellular components will be packaged into apoptotic bodies for macrophage uptake rather than directly released into the circulation, and to visualize this phenomenon [12] .

4.5. Cancer stem cells (CSCs)

Tumors, like normal adult tissues, contain stem cells that both self renew and give rise to differentiated progeny. They are the only cells that can maintain tumor growth indefinitely. The self-renewal properties of the CSCs are thus the real driving force behind tumor growth. The identification of markers that allow the prospective isolation of CSCs from whole tumor tissues helps to develop an understanding of several important biological properties of CSCs such as cell origin for a given tumor, signaling pathways for self-renewal and/or differentiation of CSCs, the molecules uniquely expressed on CSCs, and the mechanisms by which CSCs escape conventional therapies. Studies on these biological properties should lead to the development of therapies that target the CSC population and eliminate the 'engine' that drives tumors to grow, invade, and seed metastatic lesions [48]. Along with the tremendous advance

in the discovery of various cell surface markers distinguishing CSCs from non-CSCs, NPs are expected to direct theranostics to CSCs and improve the CSC-specific therapies. Taking the stem cell marker CD133, for example, it was found to be expressed on the surfaces of stem cells of brain cancer, breast cancer, prostate cancer, lung cancer, colon cancer, pancreatic cancer, ovarian cancer, and liver cancer [18].

5. CHALLENGES OF NANOTHERANOSTICS

Theranostic nanoplatforms with their unique capability for simultaneous imaging and treatment are the hopes of effective cancer therapy. However, before translation of nanotheranostics to their clinical application, there are a number of forbidding challenges that confront the developers of theranostic nanoplatforms. These challenges are diverse and they are all in part difficult due to the lack of physiologically relevant test-beds available to designers. It is critical that the engineering of these nanoplatforms be guided by biological considerations if they are to be translated into clinical use. The biological issues are complex and can only be duplicated by an *in vivo* system [49]. To date majority of theranostic nanomedicines are tested *in vitro* and relatively few have been investigated for *in vivo* efficacy [27]. This may be attributed to lack of access to the relevant animal models or robust collaborations with other experts in the field. This may lead sluggish dissemination of facts to the larger nanomedicine community, which further influences future step-by-step processing of nanotheranostics.

6. CONCLUSION AND PROSPECTIVE

Actually theranostics is representative of the evolution of multidisciplinary nanoscience, as a routine meeting of multiple disciplines including chemistry, material science, Electromagnetics, biology, medical physics, and oncology. Nanotheranostics will be developed in a broader sense so that therapy and diagnostics can work hand in hand. It is possible to predict high-impact advances in this field as researchers' pioneer approaches to develop nanoscale platforms with multiple functionalities [50]. It is likely that in the coming years, TNPs will emerge and enter clinical trials. Nanoparticles that can simultaneously detect, image, and treat disease may one day become the norm rather than the exception [51].

Further advancement of nanotheranostics by using multiple imaging agents to overcome the limitations of single imaging agent and combination of drugs to achieve better therapeutic efficacy is believed to be developed in the future with reliable and reproducible synthetic procedures and to be scaled up to production levels without much difficulty [52].

REFERENCES

1. Kievit FM, Zhang M, Cancer Nanotheranostics- Improving Imaging and Therapy by Targeted Delivery across Biological Barriers. *Adv Mater*, 2011, 23: H217-H247.
2. Vrdoljak E, Wojtukiewicz MZ, Pienkwoski T, Bodoky G, Berzinec P, Finek J, Topdorovic V, Borjovic N, Croitoru A, Cancer epidemiology in Central and South Eastern European countries. *Croat Med J*, 2011, **52**: 478-487.
3. Veld RH, Storm G, Hennink WE, Kiessling F, Lammers T, Macromolecular nanotheranostics for multimodal anticancer therapy. *Nanoscale*, 2011, **3**:4022–4034.
4. Melancon MP, Stafford RJ, Li C, Challenges to effective cancer nanotheranostics, *J controlled release*, 2012, **164**: 177-182.
5. Chen N, Cheng SH, Souris JS, Chen CT, Mou CY, Lo LW, Theranostic applications of mesoporous silica nanoparticles and their organic/inorganic hybrids. *J Mater chem*, 2013 , **1**: 3128–3135.
6. Mura S, Couvreur P, Nanotheranostics for personalized medicine. *Adv Drug Deliv Rev*, 2012, **64**: 1394–1416.
7. Muthu MS, Kulkarni SA, Raju A, Feng S, Theranostic liposomes of TPGS coating for targeted co-delivery of docetaxel and quantum dots. *Biomaterials*, 2012, **33**:3494-3501.
8. Chapman M, Pascu SI, Nanomedicines Design: Approaches towards the Imaging and Therapy of Brain Tumours, *J Nanomed Nanotechnol*, 2012, Access date 07/03/2014. http://dx.doi.org/10.4172/2157- 7439.S4-006.
9. Wang L, Xing H, Zhang S, Ren Q, Pan L, Zhang K, Bu W, Zheng X, Zhou L, Peng W, Hua Y, Shi J, A Gd-doped Mg-Al-LDH/Au nanocomposite for CT/MR bimodal imagings and simultaneous drug delivery. *Biomaterials*, 2013, **34**:3390-3401.
10. Shashi K, Satinder K, Bhart P, Acomplete review on liposomes. *Int Res J pharm*, 2012, **3**:10-16.
11. Kumar R, Kulkarni A, Nagesha DK, Sridhar S, *In Vitro* Evaluation of Theranostic Polymeric Micelles for Imaging and Drug Delivery in Cancer. *Theranostics*, 2012, **2**:714-722.
12. Cruciani O, Mannina L, Sobolev AP, Cametti C, Segre A, Unimproved NMR study of liposomes using 1-palmitoyl-2-oleoyl- sn-glycero-3-phosphatidylecholine as model. *Molecules*, 2006, **11**:334-344.
13. Chen MC, Cheng SH, Tri-functionalization of mesoporous silica nanoparticles for comprehensive cancer theranostics – the trio of imaging, targeting and therapy. *J Mater Chem*, 2010, **20**: 6149–6157.
14. Sen K, Mandal M, Second-generation liposomal cancer therapeutics- Transition from laboratory to clinic. *Int J pharm*, 2013,**448**: 28-43.
15. Li S, Goins B, Zhang L, Bao A, A Novel Multifunctional Theranostic Liposome Drug Delivery System: Construction, Characterization, and Multimodality MR, Near-infrared Fluorescent and Nuclear Imaging. *Bioconjugate chem*, 2012, **23**:1322-1332.
16. Sailor MJ, Park JH, Hybrid Nanoparticles for Detection and Treatment of Cancer. *Adv Matt*, 2012, **10**:1-24.
17. Sukumar UK, Bhushan B, Dubey P, Matai I, Sachdev A, Packirisam G, Emerging applications of nanoparticles for lung cancer diagnosis and therapy. *Int Nano Lett*, 2013, **3**:1-17.
18. Han N, Yang YY, Wang S, Zheng S, Fan W, Polymer-based Cancer Nanotheranostics- Retrospectives of Multi-Functionalities and Pharmacokinetics, *Curr Drug Metabolism***,** 2013, **14:**1-14.
19. Yuan J, Zhang H, Kaur H, Oupicky D, Peng F, Synthesis and characterization of theranostic poly(HPMA)-c(RGDyK)-DOTA-^{64}Cu copolymer targeting tumor angiogenesis-tumor localization visualized by positron emission tomography. *Mol Imaging*, 2013, **12**: 1-10.
20. Wolinsky JB, Grinstaff MW, Therapeutic and diagnostic applications of dendrimers for cancer treatment. *Adv Drug Deliv Rev*, 2008, **60**: 1037–1055.
21. Fernandez A, Manchanda R, McGoron AJ, Theranostic Applications of Nanomaterials in Cancer- Drug Delivery, Image-Guided Therapy, and Multifunctional Platform. *Appl Biochem Biotechnol*, 2011, **165**:1628–1651.
22. Zhang L, Gu FX, Chan JM, Wang AZ, Langer RS, Farokhzad OC, Nanoparticles in Medicine: Therapeutic Applications and Developments. *Clin Pharmacol Ther*, 2008, **83**:761-769.

 ISSN: 2250-1177 CODEN (USA): JDDTAO

23. Majoros IJ, Williams CR, Becker A, Baker JR, Methotrexate delivery *via* folate targeted dendrimer-based nanotherapeutic platform. *Rev Nanomed Nanobiotechnol*, 2009, **1**:502-510.
24. Doria G, Conde J, Veigas B, Giestas L, Almeida C, Assuncao M, Rosa J, Baptista PV, Noble metal nanoparticles for biosensing applications. *Sensors*, 2012, **12**:1657-1687.
25. Conde J, Doria G, Baptista P, Noble Metal Nanoparticles Applications in Cancer. *J Drug Deliv*, 2012, Article ID 751075.
26. Wang LS, Chuang MC, Ho JA, Nanotheranostics – a review of recent publications. *Int J nanomed*, 2012, **7**:4679-4695.
27. Choi KY, Liu G, Lee S, Chen X, Theranostic nanoplatforms for simultaneous cancer imaging and therapy- current approaches and future perspectives, *nanoscale*, 2011, **4**: 330-342.
28. Mukherjee S, Chowdhury D, Kotcherlakota R, Patra S, Bhadra MP, Sreedhar B, Ranjan PC, Potential Theranostics Application of Bio-Synthesized Silver Nanoparticles (4-in-1 System).*Theranostics*, 2014, **4**: 316-335.
29. Kateb B, Chiu K, Black KL, Yamamoto V, Khalsa B, Ljubimova JY, Ding H, Patil R, Portilla-Arias JA, Modo M, Moore DF, Farahani K, Okun MS, Prakash N, Neman J, Ahdoot D, Grundfest W, Nikzad S, Heiss JD, Nanoplatforms for constructing new approaches to cancer treatment, imaging, and drug delivery-What should be the policy? *Neuroimage***,** 2011, **54:** s106-s1024.
30. Ho YP, Leong KW, Quantum dot-based theranostics. *Nanoscale*,2010.**2**:60-68.
31. Liu L, Miao Q, Liang G, Quantum Dots as Multifunctional Materials for Tumor Imaging and Therapy. *Materials*,2013, **6**:483-499.
32. Singh I, Rehni AK, Kumar P, Kumar M, Aboul-Enein HY, Carbon Nanotubes- Synthesis, Properties and Pharmaceutical Applications. *Fullerenes, Nanotubes and Carbon Nano*, 2009, **17**: 361–377.
33. Zhou Z, Liposome Formulation of Fullerene-Based Molecular Diagnostic and Therapeutic Agents. *Pharm*, 2013, **5**:525-541.
34. Xie J, Liu G, Eden HS, Ai H, Chen X, Surface-Engineered Magnetic Nanoparticle Platforms for Cancer Imaging and Therapy. *Acc Chem Res*, 2011, **44**: 883–892.
35. Santra S, Kaittanis C, Grimm J, Perez JM, Drug/dye-loaded, multifunctional iron oxide nanoparticles for combined targeted cancer therapy and dual optical/magnetic resonance imaging. *Small J organ* , 2009, **5** (16): 1862–1868.
36. Vivero-Escoto JL, Huang YT, Inorganic-Organic Hybrid Nanomaterials for Therapeutic and Diagnostic Imaging Applications. *Int J Mol Sci*, 2011, **12**:3888-3927.
37. He Q, Ma M, Wei C, Shi J, Mesoporous carbon silicon-silica nanotheranostics for synchronous delivery of insoluble drugs and luminescence imaging. *Biomaterials*, 2012, **33**:4392-4402.
38. Caldorera-Moore ME, Liechty WB, Peppas NA, Responsive theranostic systems- integration of diagnostic imaging agents and responsive controlled release drug delivery carriers. *Acc Chem Res***,** 2011, **44**: 1061-70.
39. Salomir R, Palussiere J, Fossheim SL, Local delivery of magnetic resonance (MR) contrast agent in kidney using thermosensitive liposomes and MR imaging-guided local hyperthermia- A feasibility study in vivo. *J Magn Reson Imaging*, 2005,**22**: 534-40.
40. Langereis S, Geelen T, Grüll H, Strijkers GJ, Nicolay K, Paramagnetic liposomes for molecular MRI and MRI-guided drug delivery. *NMR Biomed*, 2013,**26**: 728-744.
41. Kumar C, Mohammad F, Magnetic nanomaterials for hyperthermia-based therapy and controlled drug delivery. *Adv Drug Deliv. Rev*, 2011, **63**:789–808.
42. Veiseh O, Gunn JW, Zhang M, Design and fabrication of magnetic nanoparticles for targeted drug delivery and imaging. *Adv Drug Deliver Rev*, 2010, **62**:284-304.
43. Hong B, Zu Y, Detecting Circulating Tumor Cells- Current Challenges and New Trends. *Theranostics*, 2013, **3**:377-394.
44. Ramirez IM, Garcia MG, Palakurthi S, Liu J, Application of Nanometals Fabricated Using Green Synthesis in Cancer Diagnosis and Therapy. *Green Chemi Env Benign Appr*, 2012, **6**:33-62.
45. Wang X, Li J, Wang Y, Koenig L, Gjyrezi A, Giannakakou P, Shin EH, Tighiouart M, Chen Z, Nie S, Shin DM, A Folate Receptor-Targeting Nanoparticle Minimizes Drug Resistance in a Human Cancer Model. *ACS Nano*, 2011, **5**: 6184–6194.
46. Xue X, Liang XJ, Overcoming drug efflux-based multidrug resistance in cancer with nanotechnology. *Chin j cancer*, 2012, **31**: 100-109.
47. Kunjachan S, Rychlik B, Storm G, Kiessling F, Lammersa T, Multidrug Resistance- Physiological Principles and Nanomedical Solutions. *Adv Drug Deliv Rev*, 2013, **65**: 1852-1865.
48. Ailles LE, Weissman IL, Cancer stem cells in solid tumors. *Curr Opin Biotechnol*, 2007, **18**:460-466.
49. Owens DE, Peppas NA, Opsonization, biodistribution, and pharmacokinetics of polymeric nanoparticles. *Int J Pharm*, 2006, **307**: 93-102.
50. Bardhan R, Lal S, Joshi A, Halas NJ, Theranostic Nanoshells: From Probe Design to Imaging and Treatment of Cancer. *Acc Chem Res*, 2011, 44:936-942.
51. Janib SM, Moses AS, MacKay JA, Imaging and drug delivery using theranostic nanoparticles. *Adv Drug Deliv Rev*, 2010, **62**:1052-1063.
52. Mitra RN, Doshi M, Zhang X, Tyus J, Bengston N, Santra S, An activatable multimodal/multifunctional nanoprobe for direct imaging of intracellular drug delivery. *Biomaterials*, 2012, **33**:1500-1508.

 ISSN: 2250-1177 CODEN (USA): JDDTAO