Editorial

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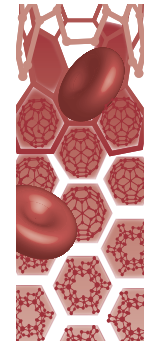
Nanomedicine



Nanotheranostics: advanced nanomedicine for the integration of diagnosis and therapy

"Nanotheranostics may be able provide in near future a practical solution for cancer and other fatal diseases to cure or at least treat them in their earliest stage."

Keywords: cancer nanotechnology • drug targeting • molecular biomaterials • molecular imaging • pharmaceutical nanotechnology • theranostics

Nanotherapeutics is to apply and further develop the various nanomedicine strategies such as polymer conjugations, dendrimers, micelles, liposomes, metal and inorganic nanoparticles, carbon nanotubes, nanoparticles of biodegradable polymers for sustained, controlled and targeted co-delivery of diagnostic and therapeutic agents for better theranostic effects and fewer side effects. The purpose is to diagnose and treat the diseases at their earliest stage, when the diseases are most likely curable or at least treatable.

Nanomedicine can be defined as application and further development of nanotechnology to solve the problems in medicine, that is, to diagnose, treat and prevent diseases at the cellular and molecular level [1]. 'Theranostics' refers to simultaneous integration of diagnosis and therapy. The term derived from thera(py) + (diag)nostics to merge the two fields for advanced applications [2]. Nanomedicine is to apply and further develop the various nanocarriers may include polymer conjugations, dendrimers, micelles, liposomes, metal and inorganic nanoparticles (i.e., noble metal, mesoporous silica nanoparticles, metal oxide, magnetic nanoparticles and quantum dots), nanocarbons and nanoparticles of biodegradable polymers for sustained, controlled and targeted co-delivery of diagnostic and therapeutic agents to diagnose and treat the diseases at their earliest stage, when the diseases are most likely curable or at least treatable [3]. It can be promising even for the fatal diseases such as cancer, cardiovascular diseases and AIDS, and creates the chance to make treatment much less troublesome and prognosis bright, thus saving resources and enhancing the quality of life for the patients [4].

Theranostic nanomedicine means colloidal nanoparticles ranging in sizes from 1 to 1000 nm (1 µm). They consist of macromolecular materials/polymers/carbon nanomaterials/metals and inorganic nanoparticles in which the diagnostic and therapeutic agents are adsorbed, conjugated, entrapped and encapsulated for diagnosis and treatment simultaneously at the cellular and molecular level. Indeed, some nanomedicines have unique physicochemical properties that show applications in diagnosis and therapy such as optical properties, hyperthermia effect and photothermal ablation. For example, gold nanoparticles, magnetic nanoparticles or carbon nanotubes have intrinsic diagnostic and therapeutic properties. They act as self theranostic nanomedicines or platforms. An ideal theranostic nanomedicine would target at the diseased site, diagnose morphology and biochemical changes of the tissue/organ of interest, provide potent/effective therapy as well as possess biocompatibility and biodegradability. The theranostics field is expected to contribute to patient healthcare and safety as personalized medicine [3,4]. This editorial was carried out with a view to summarize the recent developments of advanced theranostic nanomedicine.

Theranostic nanomedicine may be defined as nanomedicine that combines therapeutics and diagnostics in a nanocarrier [3]. The therapeutic agents include chemical drugs or biological drugs (i.e., proteins and peptides). The diagnostic agents commonly

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used in theranostic nanomedicine include fluorescent dyes or quantum dots, superparamagnetic iron oxides, radionuclides and heavy elements such as iodine. The advanced theranostic nanomedicines conjugated with targeting moiety can recognize specific target, bind to specific receptors on the targeted cell membrane and be internalized by the diseased cells via receptor-mediated endocytosis. The nanomedicine of appropriate size and surface coating can have prolonged half-life in the circulation after intravenous administration. It was observed that nanomedicines in the size range of 100–200 nm with hydrophilic surface modifications such as polyethylene glycol (PEG) and D-α-tocopherylpolyethylene glycol 1000 succinate (vitamin E TPGS or simply TPGS) are commonly used with best effects for *in vivo* applications [5–7]. For example, we have reported docetaxel loaded polylactic acid-D-α-tocopheryl PEG 1000 succinate (PLA-TPGS) nanoparticles having hydrophilic surface modification that can achieve a 360 h effective chemotherapy in comparison with only 22 h for Taxotere® after intravenous administration [8]. In recent work, we investigated the effects of the PEG chain length of the TPGS on the cellular uptake efficiency and found that shortest PEG tethering chain length, that is, PEG 1000, could have the highest cellular uptake of the nanoparticles due to their highest surface energy to overcome the bending energy needed for the detached piece of cell membrane bilayer to rap the nanomedicine into the biological cells by the mechanism of endocytosis [9].

Advanced theranostic nanomedicine is multifunctional in nature, capable of diagnosis and delivery of therapy to the diseased cells with the help of targeting ligand and biomarkers. The multifunctional capabilities include sustained/controlled release, targeted delivery, higher transport efficiency by endocytosis, stimulus responsive agent release, synergetic performance such as combination therapy and siRNA co-delivery, multimodality diagnosis and/or therapies, and quality performances such as oral delivery, escape from multidrug resistance (MDR) and intracellular autophagy [3]. Encapsulation of a single diagnostic or therapeutic agent in nanomedicine may not have high efficacy/specificity/sensitivity. Multimodality nanotheranostics is thus developed to co-encapsulate multiple diagnostic and therapeutic modes in a single nanomedicine platform [10–12].

Interestingly, siRNA can also be included in theranostic nanomedicine as an inhibitor of theranostic resistance. The siRNA-based theranostic nanomedicine has shown greatly improved diagnosis and treatment as a multimodality therapy [13].

As a novel approach, nanomedicine has also been developed for oral chemotherapy. We have reported TPGS-based nanomedicine for oral delivery of chemotherapeutic agents (e.g., docetaxel and paclitaxel) with enhanced oral bioavailability [14]. Oral delivery of theranostic nanomedicine (i.e., oral theranostics) will be a task for future research, which will radically promote the practice of cancer theranostics and improve the quality of life for cancer patients, realizing patients' dream of chemotherapy at home [15].

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Intracellular autophagy is a catabolic process in which intracellular degradation of dysfunctional cellular components or foreign invaders occurs in lysosomes. Also, intracellular autophagy affects nanomedicine after endocytosis and thus its therapeutic effect by changing intracellular pharmacokinetics of nanomedicine (i.e., intracellular absorption, distribution, metabolism and excretion of nanomedicine). Therefore, autophagy inhibitors loaded in the theranostic nanomedicine can enhance the efficiency of nanotheranostics. For example, Zhang *et al.* prepared cholic acid-conjugated PLGA nanoparticles with co-administration of autophagy inhibitors such as 3-methyladenine and chloroquine. The IC50 values of the docetaxel formulated in PLGA nanoparticles in combination with 10 mM 3-methyladenine or 30 mM chloroquine are found 5.7- or 8.0-fold more effective for the nanoparticle drug delivery after 24 h treatment. The xenograft tumor volume of the severe combined immunodeficiency (SCID) mice after 20 days of treatment with the PLGA nanoparticles formulation combined with 3-methyladenine or chloroquine was found to be only about a half in comparison with the PLGA nanoparticles formulation only [16].

In our earlier publications, we demonstrated PLA-TPGS co-polymer-based theranostic platforms. A good example of PLA-TPGS-based theranostic is PLA-TPGS and acid-functionalized TPGS-COOH copolymer blend nanoparticles prepared with folate targeting. The nanoparticles were loaded with both docetaxel and quantum dots. The targeting effect of quantum dots loaded PLA-TPGS/TPGS-COOH nanoparticles was studied in both MCF-7 breast cancer cells, which that overexpresses folate receptors, and NIH-3T3 fibroblast cells, which are expressing a low quantity of folate receptors. The studies showed higher internalization/cytotoxicity of folate-decorated, quantum dots loaded with PLA-TPGS/TPGS-COOH nanoparticles by MCF-7 breast cancer cells than by the NIH 3T3 fibroblast cells [17].

Later, we developed a multimodal imaging system by co-encapsulating superparamagnetic iron oxide nanoparticles for MRI and quantum dots for fluorescence imaging. The nanoparticles of PLA-TPGS were fabricated to combine their advantages and to promote a sustained and controlled imaging with passive targeting to the cancer cells. This novel strategy reduced the toxicity of the individual contrast agents and improved their biocompatibility and cellular uptake. The xenograft model was also conducted for biodistribution of the quantum dots and iron oxides-loaded PLA-TPGS nanoparticles among the various organs, which showed greatly enhanced tumor imaging. The *ex vivo* fluorescent images analysis showed the significant percentage fluorescent intensity increase of 67.1% in liver, 51.5% in kidney and 152.8% in tumor. The surface adsorption of nanoparticles in blood–brain barrier showed more fluorescent signal for brain samples than other organs. Also, percentage fluorescent intensity increase in brain was observed less for treated group owing to poor improvement in biodistribution of the quantum dots and iron oxides-loaded PLA-TPGS nanoparticles across the blood–brain barrier. The multimodal imaging system shows great advantages of both contrast agents making the resultant probe highly sensitive with good depth penetration for longer duration up to 6 h, which confirms the diagnosis obtained from each individual imaging [18].

Muthu *et al.* prepared TPGS-coated theranostic liposomes containing docetaxel and quantum dots with and without targeting moieties. Folic acid was used as targeting probe to target folate receptor overexpressing MCF-7 breast cancer cell lines. The higher cellular uptake and cytotoxicity of targeted theranostic liposomes was observed in comparison to non-targeted liposomes [19]. In another study, theranostic TPGS micelles containing superparamagnetic iron oxides were prepared for diagnosis and therapy of cancer. It had improved thermal and magnetic properties, *in vitro* cellular uptake, cytotoxicity and *in vivo* imaging effects in comparison to commercial Resovist® and Pluronic F127 micelles. The prepared TPGS micelles were found to be highly monodisperse, suitable size range and stable. The cellular uptake and cytotoxicity were investigated *in vitro* with a MCF-7 breast cancer cell line for 24 h. Cell viability was decreased after hyperthermia treatment using micelles. Also, T2-mapped images of xenograft grown on SCID mice showed that iron oxide-loaded TPGS micelles had approximately 1.7-times and 1.05-times T2 decrease at the tumor site compared with Resovist and Pluronic F127 micelle formulation, respectively [20].

The main challenge in current nanotheranostics includes development of new molecular biomaterials of high performance in co-formulation of diagnostic and theranostic agents; identification of new biomarkers of for the targeted disease of high specificity; investigation of possible agonism and antagonism between the diagnostic and theranostic agents co-formulated in a single nanocarriers; and intracellular autophagy and its inhabitation of nanotheranostics. Nanotheranostics may be able provide in near future a practical solution for cancer and other fatal diseases to cure or at least treat them in their earliest stage.

Financial & competing interests disclosure

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