



REVIEW

# Nanoconfinement-mediated cancer theranostics

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**Abstract** Despite various therapeutic or diagnostic developments, cancer is still one of the most lethal diseases due to insufficiently adequate treatments and the delay of the early stage of disease detection. An image-guided drug delivery system (IGDDS), as a real-time noninvasive imaging assessment of therapeutic response, has the strong potential to improve the diagnosis and treatment of cancer because its imaging property offers the quantification of nanomedicine at the intended disease sites, the possible assurance of adequate treatment and elimination of undesirable delay of early-stage diagnosis due to low resolution. One of potential modality that overcomes these challenges could be the nanoconfinement of gold (Au) nanoparticles within other nanoparticles called "Particle-in-Particle (PIP)", which is a strong candidate of cancer treatment because of its "theranostic (therapy + diagnostics)" advantages including imaging (e.g., CT) and therapeutic hyperthermia application. In this review, we will elaborate on the current application of theranostic by nanoconfinement. Then, we will narrow down the gold nanoparticle-mediated theranostic application and its nanoconfinement advantages. Finally, the future direction for maximum nanoconfinement mediated cancer therapy will be included.

**Keywords** Nanoconfinement · Theranostics · Particle-in-Particle

## Introduction

Based on statistics from the American Cancer Society, more than 1500 Americans die cancer-related deaths each day despite the availability of chemotherapy, radiotherapy, immunotherapy, gene therapy, and anti-angiogenesis treatments (Street 2019). Despite various therapeutic or diagnostic developments, cancer is still one of the most lethal diseases due to insufficiently adequate treatments and the delay of the early stage of disease detection. An image-guided drug delivery system (IGDDS), as a real-time noninvasive imaging assessment of therapeutic response, has the strong potential to improve the diagnosis and treatment of cancer because its imaging property offers the quantification of nanomedicine at the intended disease sites, the possible assurance of adequate treatment and elimination of undesirable delay of early stage diagnosis due to low resolution (Gabizon et al. 2014; Kaelin 2005; Paci et al. 2014). However, the use of IGDDS is still limited because of the several challenges, including the lack of sufficient sensitivity and resolution of detection and the relatively low therapeutic efficacy for clinical application. In order to improve IGDDS to meet needs of clinical application, currently nanoconfinement induced contrast enhancement (NICE) (Fahmy et al. 2017) and/or nanoconfinement induced therapeutic enhancement (NITE) (Gabizon et al. 2014) has been raised the attention in the field of cancer therapy due to their potential enhanced imaging and therapeutic efficacy. One of potential modalities that encompass both NICE and NITE could be the nanoconfinement of gold (Au) nanoparticles within other nanoparticles called "Particle-in-Particle (PIP)" (Yoo et al. 2018), which is a strong candidate of cancer treatment because of its "theranostic (therapy + diagnostics)" advantages including imaging (e.g., CT) and therapeutic hyperthermia application.

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In this review, we will elaborate current application of theranostic or nanoconfinement. Then, we will narrow down the gold nanoparticle mediated theranostic application and its nanoconfinement advantages. Finally, the future direction for maximum nanoconfinement mediated cancer therapy will be included.

## Cancer theranostics

Innovative modalities having simultaneous therapy and diagnostics (“Theranostics”) have gained significant interest for real time disease imaging and its specific treatment including cancer. There have been intensive research efforts on theranostics modalities development that show their significant therapeutic and diagnostic capabilities according to their different shapes, sizes, functionalities, targeting mechanisms, and imaging modalities. The ideal design paradigm for maximum efficacy of theranostic nanoparticles includes following key components: diagnosis component for noninvasive imaging, polymer coating for nanoparticle stability and its functional bioconjugation, and drug loading capabilities. These components will be introduced into the next three subchapters as well as current clinical trials of theranostics for the last subchapter.

### Diagnosis components for noninvasive imaging

Over the several decades, various diagnosis components for noninvasive imaging have been investigated including magnetic resonance imaging (MRI) (Cademartiri et al. 2007), computed tomography (CT) (Simon 2000), positron emission tomography (PET) (Zhang et al. 2006), single-photon emission computed tomography (SPECT) (Urtasun et al. 1996), ultrasound (US) (Cheng et al. 2005) and fluorescence imaging (Artzi et al. 2011). These quantitative or semi-quantitative imaging modalities have been applied to employ highly sensitive image techniques to find out biodistribution of the labelled drugs or probe in the body. Incorporating radionuclides such as  $^{99m}\text{Tc}$ ,  $^{111}\text{In}$ , and  $^{64}\text{Cu}$  (Manrique et al. 1999; Spahn et al. 2004) into nanoparticles has been developed for noninvasive biodistribution studies through SPECT. One example of PET imaging contrast is the analog of glucose 2- $^{18}\text{F}$ -fluoro-2-deoxy-D-glucose ( $^{18}\text{F}$ -FDG) (Markou et al. 2005). Near infrared (NIR) dyes such as indocyanine green (ICG), IR-783, and IR-780 are one of examples for fluorescence imaging and they show unique optical properties due to their absorption at NIR wavelength (Kuang et al. 2017). Currently, CT contrast agent for clinical application is based on iodine-based contrast agent (Gignac et al. 2016). One of the examples includes iodinated lipid contrast agent (Lipiodol®, Guerbet) (Kweon et al. 2010). It serves as a diagnostic tool to help detect its accumulation in solid

tumors to monitor the tumor by CT. Lastly, a significant amount of research for MRI based contrast agent have been developed and among them  $\text{Gd}^{3+}$ -based MRI contrast agent have been most successful (Iwaki et al. 2012).

Although there has been extensive amount of imaging modalities developed in the past few decades, the heterogeneity of tumor and toxicity mediated dose limitation still prevent from the clinical success of disease diagnosis. To overcome this challenge, the development of cross-imaging technologies has been noticed in the biomedical imaging field. For example, CT or MRI is hybridized with SPECT/PET because CT or MRI can provide 3-dimensional structural information while SPECT/PET lacks these features (Cherry 2009; Misri et al. 2012).

### Polymer coating for nanoparticle stability and its functional bioconjugation

To target tumor sites effectively, the theranostics systems must have several requirements. First, they should be avoided by body defensive system (e.g., reticuloendothelial system: RES) to target maximum amount at the tumor sites. Second, they need to be maximumly localized in the tumor sites. To overcome these challenges, two major solutions have been introduced in the theranostic research field such as poly(ethylene glycol) (PEG) and targeting ligands coating on the surface of theranostic system (Ardana et al. 2014; Yao et al. 2016).

Once the theranostic systems are systemically administered into the patient’s body, they are passively targeted to tumor sites through the enhanced permeability and retention effect (EPR) effect (Maeda et al. 2000). During the circulation and before the passive entrance of tumor site, they must be survived. PEG allow them to extend their systemic half-life because PEG can empower the stealth property to the theranostic system (Zhang et al. 2017). Thus, prolonged circulation time of the theranostic systems enhance their passive tumor targeting capacity. Within the tumor microenvironment, the theranostic systems must be interacted with the tumor surface to expand their local delivery. By virtue of specific interaction of targeting ligand on the theranostic systems with the overexpressed receptors on the tumor cell surface (Mamot et al. 2003), enhanced tumor targeting efficacy will be achieved. It has the strong potential to result in maximum cancer theranostic outcome.

Currently, many biomarkers have been identified as possible tumor targeting receptors including the folate receptor (Zhang et al. 2012), transferrin receptors (Daniels et al. 2006), integrin (Liapis et al. 1996) and human epidermal receptor 2 (HER-2) (Nahta et al. 2004). The specific interaction between arginine-glycine-aspartic acid (RGD) peptide with avb3 integrin overexpressed on melanoma and glioblastomas allow the theranostic systems to target those tumors

cells (Chen et al. 2016). The CD71 receptor or transferrin receptor (TfR) that is abundantly expressed in neuroblastoma and MDA-MB-231 metastatic breast cancer results in enhance tumor localization by transferrin coated theranostic system (Mendes et al. 2018). Lung carcinoma A549 cells overexpress the folate receptor on their cell surface and the folic acid coated theranostic system thus can target those cells specifically (Santra et al. 2011).

### Drug loading capabilities

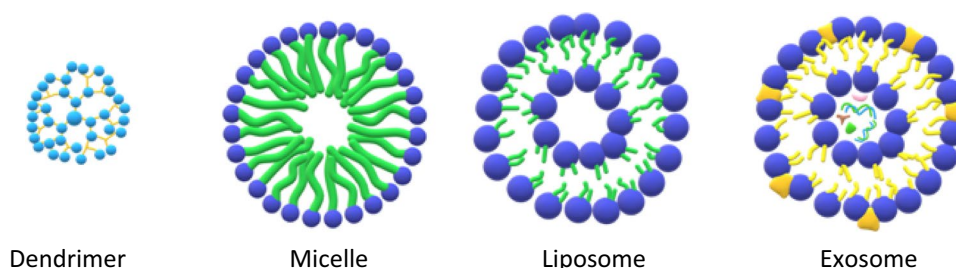
The delivery of drug and/or contrast agent by the theranostic systems is dependent on the carrier property and it is achieved by the chemical conjugation, or physical encapsulation. Biodegradable polymers that is conjugated with drugs or contrast agents is the smallest size of theranostic system. The bigger size (10–200 nm) of carrier (Fig. 1) such as dendrimer, emulsion, polymeric micelle, and liposomes encapsulate and deliver the drugs and/or contrast agents. For example, multifunctional polymeric micelles encapsulate alkynyl-DOTA-Gd as an MRI contrast agent and paclitaxel (6.67w/w% as a loading content) as an anticancer drug (Li et al. 2011a). <sup>89</sup>Zr-labeled N-(2-hydroxypropyl) methacrylamined) copolymer (HPMA) is conjugated with doxorubicin to deliver both PET contrast agent and cancer drug (Koziolová et al. 2017). By incorporation of cisplatin and 1,1'-dioctadecyl-3,3,3'-tetramethylindotricarbocyanine

iodine (DiR) into liposome, a versatile theranostic liposome for cancer therapy have been explored and the results from in vivo animal study shows efficient theranostic efficacy (Feng et al. 2016). To target and image glioma, the exosomes were loaded with curcumin and superparamagnetic iron oxide nanoparticles and were conjugated neuropilin-1-targeted peptides. The engineered exosomes provided the glioma-targeted images and therapeutic effects in vitro and in vivo (Jia et al. 2018).

### Current clinical trials of theranostics as cancer treatment

In this section, several current clinical trials of theranostics as cancer treatment in US will be introduced according to the phase of each study (Table 1). The information for this section is based on the US National Library of Medicine. Currently (September 2019), total 12 clinical trials of theranostics for cancer therapy are active and among them there is only one (US National Library of Medicine 2000a) early phase of theranostics clinical trial. In this trials, radioactive drugs such as <sup>131</sup>I-iodine and <sup>90</sup>Yttrium are used for radio therapy against neuroendocrine tumors and they can be used contrast agents for SPECT/CT. In phase 1 stage, there are active five clinical trials (US National Library of Medicine 2000c) of theranostics against thyroid cancer (2 trials), meningioma, neuroblastoma, and hepatocellular carcinoma.

**Fig. 1** Various theranostic carriers that can encapsulate and deliver therapeutic and diagnostic agents



**Table 1** Theranostic agents for cancer in current clinical trials

No	Phase	Disease	Intervention/treatment
1	Early phase 1	Neuroendocrine tumor	<sup>90</sup> Y-DOTA-3-Tyr-Octreotide <sup>131</sup> I-MIBG
2	Phase 1	Thyroid cancer	<sup>177</sup> Lu-PP-F11N
3	Phase 1	Thyroid cancer	<sup>111</sup> In-CP04
4	Phase 1 Phase 2	Meningioma	Cu-64 SARTATE and Cu-67 SARTATE
5	Phase 1 Phase 2	Neuroblastoma	Cu-64 SARTATE and Cu-67 SARTATE
6	Phase 1 Phase 2	Hepatocellular carcinoma	[ <sup>68</sup> Ga]DOTATATE and [ <sup>177</sup> Lu]DOTATATE
7	Phase 2	Prostate cancer	<sup>177</sup> Lu-PSMA617
8	Phase 2	Non-small cell lung cancer	<sup>18</sup> F-FLT-TEP
9	Phase 2	Neuroendocrine tumor	<sup>68</sup> GaDOTATOC and <sup>90</sup> YDOTATOC

First thyroid cancer trial uses the radiolabeled gastrin analogs ( $^{117}\text{Lu-DOTA-(dGlu)}_6\text{-Ala-Tyr-Gly-Trp-Nle-Asp-Phe-NH}_2$ ) as a radionuclide therapy. In this trial, the patient's neck/thorax/abdomen are scanned by CT. In the next thyroid cancer trial, radiolabeled peptide drug ( $^{111}\text{In-CP04(DOTA-(dGlu)}_6\text{-Ala-Tyr-Gly-Trp-Met-Asp-Phe-NH}_2$ ) and SPECT/CT images are the therapeutic and diagnostic components. For the trials of meningioma, Cu-64 SARTATE and Cu-67 SARTATE are PET imaging and radionuclide therapeutic components, respectively. Both Cu-64 SARTATE and Cu-67 SARTATE also used for clinical trials of neuroblastoma. The last phase 1 trial of theranostics is the assessment of  $^{177}\text{Lu-DOTATATE}$  for radionuclide therapy and [ $^{68}\text{Ga}$ ] DOTATATE for PET imaging of hepatocellular carcinoma. In phase 2, six clinical theranostic trials (US National Library of Medicine 2000b) are active including prostate cancer using  $^{117}\text{Lu-PSMA}$  as a prostate specific membrane antigen (PSMA) therapy and PET imaging, non-small cell lung cancer using  $^{18}\text{F-2-}^{18}\text{F-fluoro-2-deoxy-D-glucose}$  as a tyrosine kinase receptor inhibitor and PET imaging contrast agent, neuroendocrine tumor using  $^{90}\text{Y-DOTATOC}$  for radiotherapy and  $^{68}\text{Ga-DOTATOC}$  for PET/CT imaging, meningioma using Cu-64 SARTATE for radionuclide therapy and Cu-67 SARTATE for PET imaging, neuroblastoma using Cu-64 SARTATE for radionuclide therapy and Cu-67 SARTATE for PET imaging, and hepatocellular carcinoma using  $^{177}\text{Lu-DOTATATE}$  for radionuclide therapy and [ $^{68}\text{Ga}$ ] DOTATATE for PET imaging. Up to now, there is no phase 3 and phase 4 clinical trials of theranostics that are active now.

### Nanoconfinement advantages for cancer treatment

Nanoconfinement defines the physical confinement within a nanosized region, and it is a very new concept in therapeutic and diagnostic fields (Cipolla et al. 2016). Most of the current studies related to nanoconfinement have dealt with the physical change or enhancement after a confinement of agent within nanosized frame or capsules. For example, nanoconfined  $\beta$ -sheet allow silk to enhance its stiffness, strength, and toughness (Keten et al. 2010). From the study by Zuo et al. the glass transition temperature of ionic liquids was found to be dependent on the confinement of ionic liquid components (Zuo et al. 2019). On the contrary, there is very few researches available about nanoconfinement mediated imaging (1 paper from Pubmed by the key word of “nanoconfinement & contrast enhancement”) or therapeutic enhancement (0 research from Pubmed by the key word of “nanoconfinement & therapeutic enhancement”), indicating its infant stage of research.

In our studies, we utilized this unique nanoconfinement phenomenon in the theranostic enhancement application. Nanoconfined imaging agent within nanoparticles showed

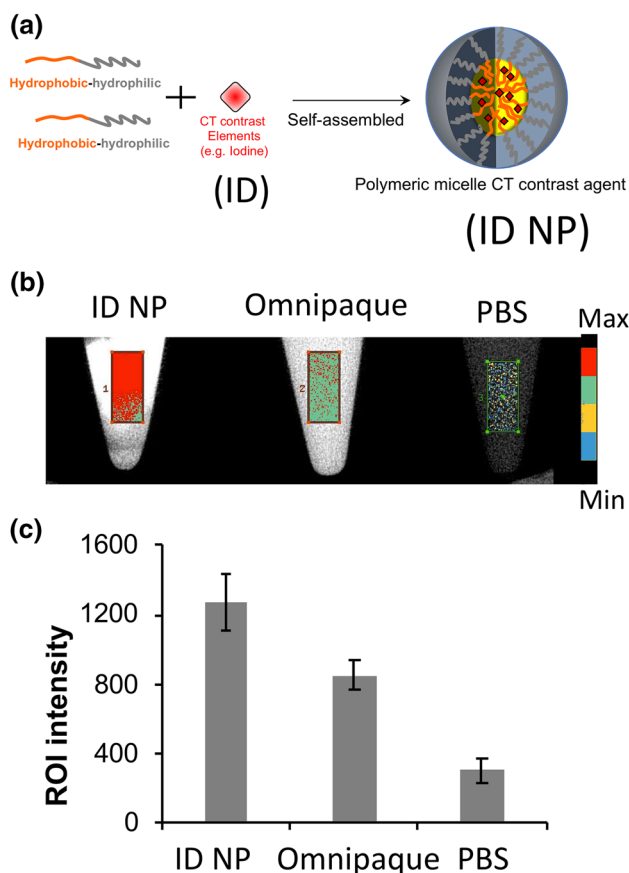
5–10 folds enhancement of imaging intensity, compared with its commercial counterpart (Fahmy et al. 2017). It provides us various advantages in the clinical application including potential dose reduction, minimum toxicity, enhanced imaging resolution, and disease detection enhancement for the early stage of disease detection. Also, gold nanoparticle encapsulated within PLGA-PEG micelle (Particle in Particle: PIP) was developed. The PIP platform contains aggregated gold nanoparticles which may allow increasing the surface area and increase the number of the nanoconfinement of gold compared to free gold nanoparticles in a given volume. Thus, this system enhances the generation of heat because the exothermic effect of the nanoparticle is depending on the surface area of each nanoparticle. On the basis of this principle, PIP revealed various advantages from nanoconfinement (Yoo et al. 2018): (i) the absorbance of PIP is able to shift to near-infra red (NIR) wavelength for the deep penetration purpose; (ii) it produces multi-folds heat production compared with individual gold nanoparticles or its clusters; and (iii) spherical gold PIP is able to hold its shape after multiple NIR applications without any loss of absorbance in NIR and heat production while gold nanorod PIP shows its shapes after multiple NIR application that leads to the loss of absorbance and heat production. Thus, nanoconfinement mediated therapeutic and diagnostic enhancement has a strong potential to relieve the burden of current clinical cancer treatment challenge. In this regard, we will introduce several examples of both nanoconfinement induced contrast or therapeutic enhancement at the following subchapters although very few researches are existed.

### Nanoconfinement induced contrast enhancement

Although nanoconfinement is well recognized phenomenon, the contrast enhancement by nanoconfinement in Pubmed shows two literatures (Ho and Wang 2019; Law et al. 2014). Both papers are not directly related with imaging enhancement. However, there are few researches appeared in the Google and they are 2 papers and 1 patent related with NICE. The study by Tuyen Duong et al. (Nguyen et al. 2018) elaborates that nanoconfinement of iron oxide within poly(L-lactic-co-glycolic acid) (PLGA) (PLGA/SPION). Then, PLGA/SPIONs are encapsulated within liposome to make hybrid nanoconstruct that enhances magnetic relaxivity and thus it is able to image mouse osteosarcoma tumor by MRI. Also, another study demonstrates that the confinement of magnetic resonance contrast agents within polymer nanocontainers enable an increased relaxivity compared to an aqueous solution of the contrast agent. It applies successfully in vivo to yield enhanced contrast in MRI imaging (Malzahn et al. 2016).

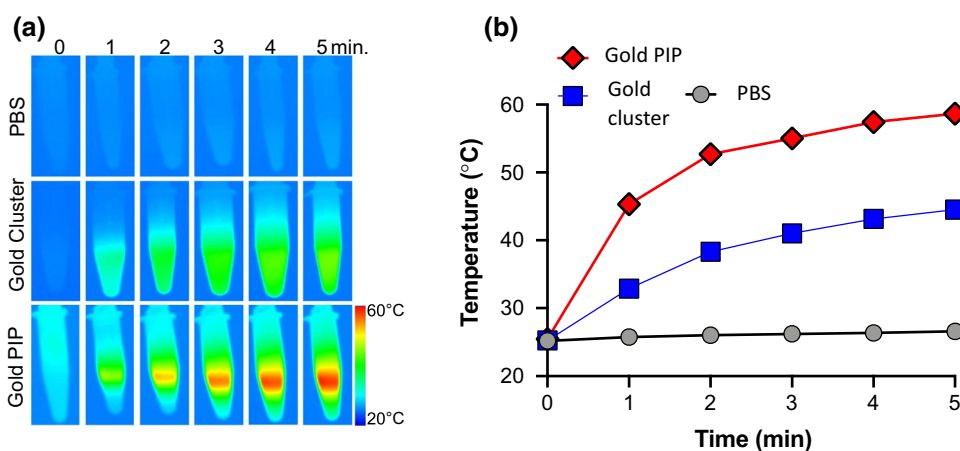
The only patent (Fahmy et al. 2017) that described NICE is about the CT or MRI contrast agent. Specifically, iodine

CT contrast agent or iron oxide MRI contrast agent are encapsulated into the polymeric nanoparticle to make Particle-in-Particle system and their CT or MRI contrasts are significantly enhanced (Fig. 2). It allows for the use of lower concentration of contrast agent which avoids the toxicity associated with high concentration of such agents.



**Fig. 2** Iodine encapsulated PLGA-PEG nanoparticles were scanned under micro CT (a). Schematic picture of iodine encapsulated nanoparticles (b). Micro CT images of each sample (c)

**Fig. 3 a** The temperature from gold nanoparticles encapsulated PLGA-PEG nanoparticles (Particle-in-Particle) systems was determined by thermal camera. **b** The results from (a) were plotted



**Nanoconfinement induced therapeutic enhancement (NITE)**

Compared with NICE, NITE has been actively studied. Although there is no literature appeared in the Pubmed using “nanoconfinement” and “therapeutic enhancement”, a couple of researches in the Google were found. The first study that was done by our lab is about the gold nanoparticle encapsulated within PLGA-PEG micelles, called Particle-in-Particle (PIP) system as an anticancer hyperthermia (Yoo et al. 2018) (Fig. 3). The results from this study show the significant heat production from PIP that suppress various cancer cells (Yoo et al. 2018). Also, iron oxide nanoparticle cluster encapsulated PLGA nanoparticles demonstrate higher transverse relaxivity, leading to enhance the pharmacological activity (Ragheb et al. 2013).

**Gold nanoparticle and its PIP for nanoconfinement theranostic application**

Gold nanomaterials such as spherical nanoparticles (AuNP), nanorods (AuNR), nanocages, and nanoshells (AuNS) have been designated as multi-functional probes due to their unique properties of optical quenching, X-ray absorption, and surface-enhanced raman scattering (SERS) (Boisselier and Astruc 2009; Huang et al. 2006). These sensing properties are applied to single diagnostic imaging techniques, but additional gold nanomaterial properties like size controllability, excellent biocompatibility, easy surface modification, and photothermal effects can be further used towards multi-purpose theranostic agents (Boisselier and Astruc 2009; Chithrani et al. 2006).

The gold nanoparticles have been used in cancer imaging as various different ways. First, since gold has a significant X-ray attenuation coefficient than other elements in human bodies, the accumulation of gold nanoparticles in tumors is able to increase X-ray attenuation for CT images of tumors. Thus, targeting labelled gold nanoparticles can



be potential CT contrast agents (Aydogan et al. 2010). As a second example of gold nanoparticle for cancer imaging, it can be used as a light scattering-based imaging contrast agent. Generally, gold nanoparticles can scatter light according to their shape and size. Gold nanoparticles with greater size of 10 nm can be visualized by dark-field scattering microscopy and they are more photostable than a fluorescent dye (Huang et al. 2006). The third example of cancer imaging by gold nanoparticles include their application of the photoacoustic imaging (PAI) (Wang and Lu 2017). It is based on the acoustic waves generated by the thermal expansion of gold nanoparticles induced by optical excitation. The images of PAI are derived from the ultrasonic waves detection after pulsed laser irradiation. Gold nanoparticles have strong potential for PAI due to their photothermal conversion ability and tunable optical properties. The gold nanorods are able to visualize the mice ovarian cancer using PAI (Jokerst et al. 2012).

Most of gold nanoparticles as therapeutic purpose have been applied as photothermal therapy because of their production of heat upon external energy source such as laser. The extent of heat generation is directly proportional to the incident excitation power and the surface properties, shape, and size of gold nanoparticles. For example, spherical gold nanoparticles produce heat upon 500–600 nm wavelength of laser (Bernardy et al. 2010), while gold nanorod does upon near-infrared (NIR) laser (Dickerson et al. 2008).

The theranostic applications of gold with modifications have been demonstrated. Glycol chitosan AuNP (GC-AuNP) with matrix metalloproteinase (MMP)-sensitive peptide probes have been used for multimodal tumor imaging: (1) contrasted CT images of the tumor and (2) optical images of tumor region by fluorescence Cy5.5 (Sun et al. 2011). Nucleic acids integrated AuNS was demonstrated as theranostic probes for phototriggered siRNA delivery (Lee et al. 2014). PEG-coated AuNR (PEG-AuNR) was reported as a CT contrast agent as well as a therapeutic photothermal agent (Von Maltzahn et al. 2009). When NIR laser or high-intensity focused ultrasound was applied to raise the temperature of the medium (higher than the melting temperature of the phase-change material), the encapsulated molecules were released from the inside of the Au nanocage (Li et al. 2011b; Rey et al. 2010).

In our study, we have demonstrated comprehensively that nanoconfinement of imaging agent or gold leads to the significant enhancement of image intensity and temperature elevation. However, these study results are not optimized for ideal gold-based theranostics, and they are from a segregated individual study of each aspect such as diagnostics and therapeutics. Thus, we need to develop and optimize a gold-based theranostics that integrates these elements within one simple nanoparticle system to maximize the chance of its clinical application.

## Future direction and summary

Although versatility of gold nanoparticles allow them to have strong potential to be an theranostics candidate, they still have limits to be developed into an ideal theranostics for clinical application because of the following unmet requirements: unsatisfactory imaging resolution to distinguish disease from surrounding tissues, insufficient heat production for hyperthermia, and low sensitivity against NIR for deep tissue penetration capability (Deatsch and Evans 2014; Wang et al. 2015). From the previous chapter about the clinical trials of theranostics, there are also no nanoparticle related trials but mostly drug and/or contrast imaging conjugates. Thus, it is of substantial clinical importance to develop a new gold-based theranostics that can support high enough imageable system and produce sufficient hyperthermia.

One of potential solution will be taking advantage of nanoconfinement of gold PIP as an innovative theranostic cancer treatment because it is able to produce multifold thermal energy as a hyperthermia cancer therapy and it also can enhance cancer imaging capability by nanoconfinement. The other potential solution could be decoration of specific tumor targeting antibody that is produced by cancer exosome. Since cancer exosomes resemble with mother cancer cell surface, the injection of these cancer exosome will be able to produce the potential antibody candidates that specifically target exosome surface. Thus, these antibodies also can specifically target mother cancer cell surface.

In summary, combining both nanoconfinement advantage of PIP system and cancer cell exosome mediated antibody coating has strong potential of clinical transfer of theranostic cancer treatment.

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