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Supramolecular Nanodevices: From Design Validation to Theranostic Nanomedicine

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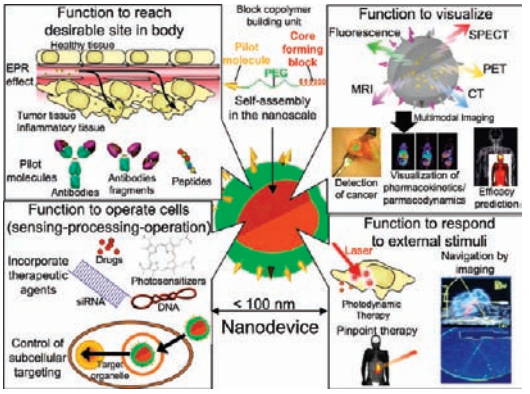

The increasing importance of nanotechnology in the biomedical field and the recent progress of nanomedicines into clinical testing have spurred the development of even more sophisticated nanoscale drug carriers. Current nanocarriers can successfully target cells, release their cargo in response to stimuli, and selectively deliver drugs. More sophisticated nanoscale carriers should evolve into fully integrated vehicles with more complex capabilities. First, they should be able to sense targets inside the body and adapt their functions based on these targets. Such devices will also have processing capabilities, modulating their properties and functions in response to internal or external stimuli. Finally, they will direct their function to the aimed site through both subcellular targeting and delivery of loaded drugs. These nanoscale, multifunctional drug carriers are defined here as nanodevices. Through the integration of various imaging elements into their design, the nanodevices can be made visible, which is an essential feature for the validation. The visualization of nanodevices also facilitates their use in the clinic: clinicians can observe the effectiveness of the devices and gain insights into both the disease progression and the therapeutic response. Nanodevices with this dual diagnostic and therapeutic function are called theranostic nanodevices.

In this Account, we describe various challenges to be overcome in the development of smart nanodevices based on supramolecular assemblies of engineered block copolymers. In particular, we focus on polymeric micelles. Polymeric micelles have recently received considerable attention as a promising vehicle for drug delivery, and researchers are currently investigating several micellar formulations in preclinical and clinical studies. By engineering the constituent block copolymers to produce polymeric micelles that integrate multiple smart functionalities, we and other researchers are developing nanodevices with favorable clinical properties.

Introduction

In the past two decades, enormous effort has been devoted to the development of nanoscale carriers that selectively deliver bioactive substances to diseased sites such as malignant cancers.[1−6] Nanoscale carriers can maximize the therapeutic efficacy and minimize the side effects of loaded drugs. Particularly, subhundred-nanometer-scale vehicles are known to accumulate selectively in solid

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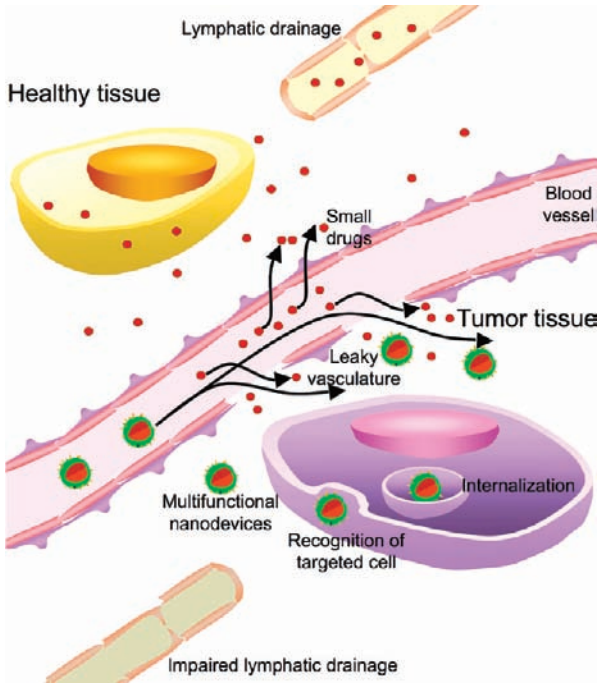

FIGURE 1. Enhanced permeability and retention (EPR) effect. Neovasculature of tumors differs greatly from that of normal tissues. Endothelial cells in tumor blood vessels are poorly aligned or disorganized with large fenestrations, causing macromolecules to leak extensively into the tumor tissue. In addition, slow venous return in the tumor tissue and poor lymphatic clearance cause macromolecules to be retained in the tumor. This effect does not apply to low-molecular-weight drugs because of their diffusion into the entire body and rapid renal clearance.

tumors due to vascular hyperpermeability and impaired lymphatic drainage,[1−6] which is termed the enhanced permeability and retention (EPR) effect (Figure 1).[7] Indeed, several nanoscale carrier formulations such as Doxil and Abraxane are already in clinical use.[8−11]

Today, nanoscale carriers can successfully achieve cellular targeting, programmable release of their cargo and selective delivery of the drugs.[1−6] Their evolution into nanodevices will rely on the consistent integration of the following multiple functions: (1) sensing (detecting targets inside the body and adapting their function based on these targets), (2) processing (modulating their properties and functions responding to internal or external stimuli), and (3) operation (properly performing the desired task in a spatiotemporally controlled manner in the body). Such nanodevices can be embodied by the "bottom-up" approach through nanoscale integration of functional components such as therapeutic and imaging agents, synthetic polymers and peptides and proteins. Considering viruses as an utmost natural example, self-assembly is an efficient process taking advantage of nature's way for construction of smart nanodevices. Nanodevices are a key platform to innovate on the existing methodologies of not only clinical diagnosis and therapy but also drug development and basic life sciences.

Imaging function can be integrated into the multifunctionality of nanodevices. The modalities for imaging include optical imaging, computed tomography (CT), ultrasound (US), magnetic resonance imaging (MRI), and nuclear imaging including single photon emission computed tomography (SPECT) and positron emission tomography (PET). Such imaging function provides the methodologies to appropriately evaluate in vivo performances of nanodevices, which are designed to exert multiple smart functions (i.e., sensing, processing and operation) in the body. In this regard, recent advances in intravital imaging technologies such as in vivo confocal microscopy facilitates in situ evaluation of nanodevices.[12,13] Thus, integration of an imaging function into nanodevices can validate the design strategy of multifunctional nanodevices, which should be essential to their optimization and further functionalization for in vivo applications. From the clinical standpoint, nanodevices with imaging function can enhance the visibility of specific tissues by increasing the signal-to-noise ratio relative to the surrounding tissues, offering ultrasensitive diagnosis against small lesions, which are undetectable by current diagnostic methods. The incorporation of different contrast agents into nanodevices enables multimodal imaging that can improve the precision of diagnosis by exploiting advantages of each imaging modality.[14,15] Furthermore, increasing attention has recently been paid to functional imaging to detect specific environments (e.g., acidic pH conditions in solid tumors), cellular responses (e.g., proliferation and apoptosis), and chemical reactions (e.g., enzymatic reactions), allowing for evaluating biological responses to specific treatments.[16,17]

In this Account, we describe the challenges in the development of more sophisticated nanodevices based on supramolecular assemblies of engineered block copolymers and discuss the concept and significance of theranostic nanodevices. In particular, we focus on polymeric micelles with core−shell architecture as practical platforms for integrating multiple functionalities.[4−6] Polymeric micelles possess ideal properties to be used as drug carriers, such as prolonged blood circulation and enhanced accumulation in solid tumors, and several micelle formulations incorporating anticancer agents have advanced to clinical studies.[18,19]

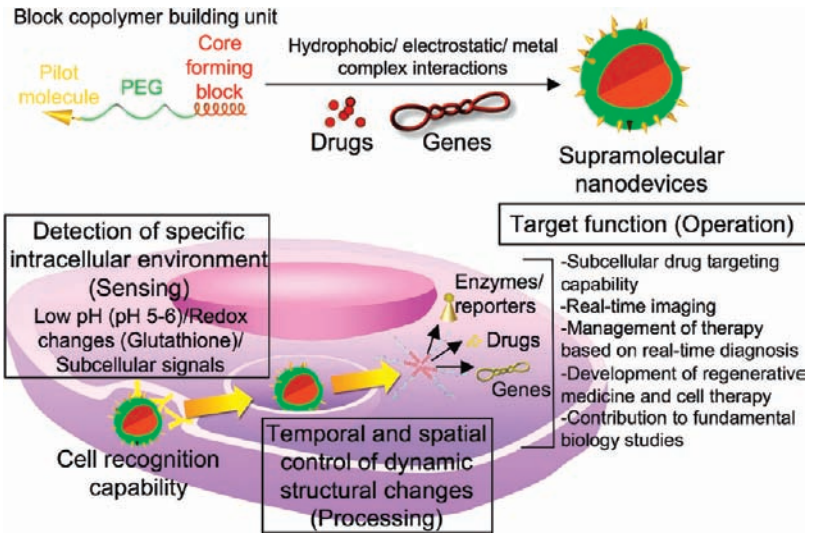

FIGURE 2. Supramolecular nanodevices as a versatile platform for cell therapy. Nanodevices can be designed to perform three functions: (1) sense specific intracellular environments; (2) process (modulate their properties and functions) responding to internal or external stimuli; and (3) operate properly at the desired site.

Integration of Functional Imaging into the Design of State-of-the-Art Nanodevices

The integration of multiple smart functions into a nanodevice platform can improve targeting to diseased sites and enhance diagnostic and therapeutic efficacies (Figure 2). These nanodevices can be designed to reach desirable sites in the body by introducing pilot molecules on their surface in addition to the control of their physicochemical parameters including size, surface charge, and stability.[1−6] Also, nanodevices are aimed to control the subcellular distribution of delivered drugs and to activate the drugs in an environmentally sensitive or external-stimuli-responsive manner.[1−6] Furthermore, nanodevices are expected to efficiently deliver plasmid DNA and siRNA to the target organelles in the cell and act as a safe and efficient nonviral vector.[20,21] Despite these advances, however, it remains controversial whether multifunctional nanodevices actually work as designed inside the body. Integrating an imaging function into the nanodevice design can enable researchers to address this uncertainty by performing in vivo evaluation of nanodevice performance, thus validating design strategies as well as facilitating optimization and further functionalization.

Recent advances in imaging technologies to assist in in vivo validation of nanodevices include whole-body imaging systems and in vivo confocal microscopy. Whole-body luminescent and near-infrared fluorescent imaging enable researchers to follow, in real time, the biodistribution of nanodevices,[22,23] validate targets,[24−26] identify subcellular trafficking pathways,[27] determine mechanisms of action, and monitor disease progression in living animals.[28,29] To enable visualization of whole-body distribution and bioavailability, nanodevices can be labeled with fluorescent dyes and quantum dots[30,31] and equipped with near-infrared probes for deep tissue imaging using contrast enhancement.[32] Intravital confocal microscopy provides instant histopathology at the cellular and subcellular levels and therefore is ideal for investigating dynamic events under in vivo conditions.[12,13,33] The technique can be used to visualize the distribution and clearance of nanodevices within various tissues and organs (Figure 3A) and is particularly effective for investigating dynamic and complex events such as blood circulation, site-specific drug accumulation, subcellular trafficking, and overcoming of biological barriers.[12] Moreover, the biological features of nanodevices can be observed in a straightforward manner. For example, direct visualization of the dynamic behavior of DNA polyplexes during circulation has demonstrated that PEGylation prevents the formation of aggregates of DNA polyplexes and their subsequent interaction with platelets (Figure 3B).[13]

Nanodevices that respond to chemical and physical stimuli to achieve intracellular drug delivery are of particular recent interest.[1−6] The stimuli-responsive controlled release of their drug payload maximizes the specificity of drug action at the target site. Furthermore, stimuli-responsive nanodevices can enhance the pharmacological activity of the loaded drugs by improving pharmacokinetics at the subcellular level. It has been reported that nanodevices designed to release active drugs in acidic organelles, such as endosomes and lysosomes, might circumvent recognition by the drug efflux pump (e.g., P-glycoprotein) through

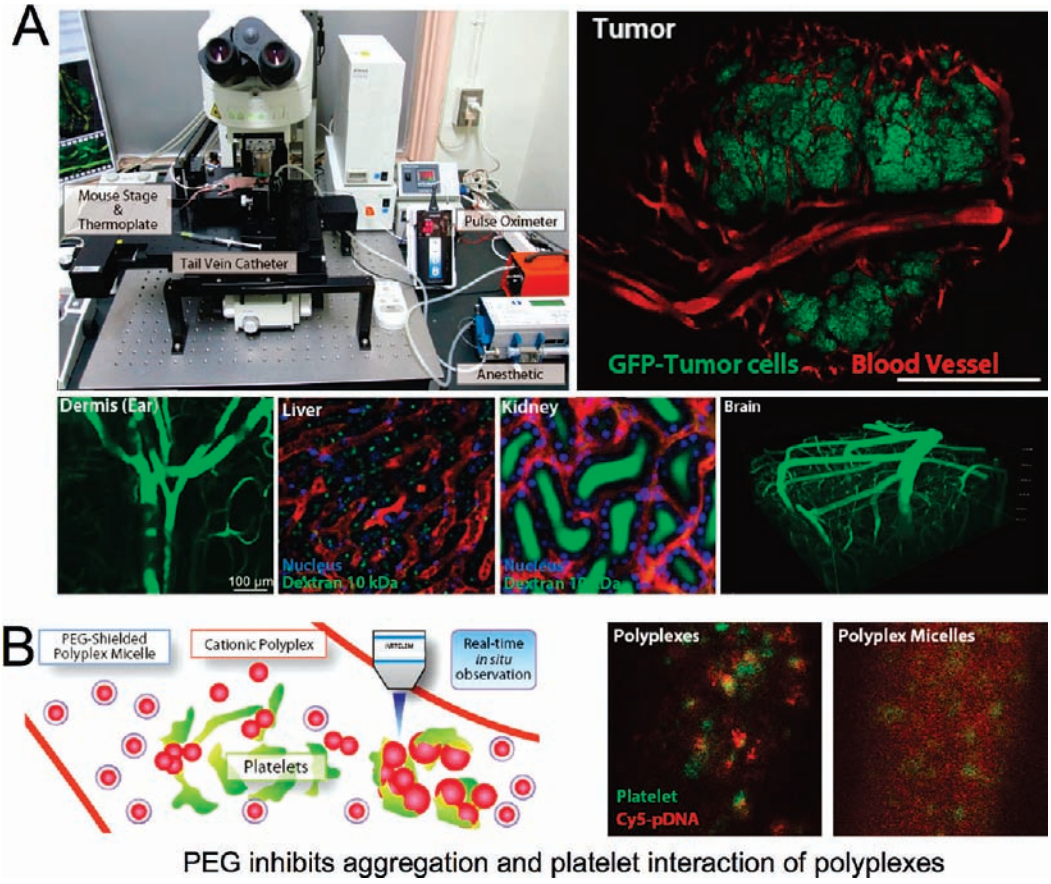

FIGURE 3. Visualization by in vivo laser confocal microscopy. (A) Scheme of in vivo laser confocal microscopy. The technique permits dynamic visualization of fluorescent molecules and biological markers at subcellular levels in tumors and healthy tissues such as ear lobe dermis, liver, kidney, or brain. Reprinted with permission from ref 12. Copyright 2010 Optical Society of America. (B) Effect of the PEGylation of DNA polyplexes observed by in vivo laser confocal microscopy. The formation of aggregates of polyplexes (red) followed by the interaction of these aggregates with platelets (green) and the prevention of these issue by PEGylation were observed in situ under the flow in a capillary. Reprinted with permission from ref 13. Copyright 2011 Elsevier.

internalization by endocytosis, thus overcoming multidrug resistance in cancer cells.[34,35]

Recently, we demonstrated that nanodevices can work as nanoscale Trojan horses to bypass drug-inactivation pathways in the cytoplasm and deliver drugs efficiently to the target nuclei, overcoming drug-resistance in cancer cells. Polymeric micelles incorporating (1,2-diaminocyclohexane)platinum(II) (DACHPt), the parent complex of anticancer drug oxaliplatin, are formed by reversible complex formation between DACHPt and poly(ethylene glycol)-*b*-poly(glutamic acid) [PEG-*b*-P(Glu)].[29,33,36] This reversible chelation allows the release of DACHPt from the micelles via ligand-substitution reaction of Pt(II) from carboxylate to chloride ion, and the release rate depends on pH and [Cl^-].[29,33,36] Accordingly, DACHPt-loaded micelles accelerate DACHPt release in the late endosomal environment close to the perinuclear region because of a decrease in pH and an increase in [Cl^-] following initial uptake into the early endosome.[33] Importantly, in vitro and in vivo studies revealed that DACHPt-loaded micelles showed remarkable antitumor activity against oxaliplatin-resistant tumors (Figure 4A). We hypothesized that DACHPt-loaded micelles may overcome the drug resistance by circumventing cytoplasmic detoxification systems that are activated in the drug-resistant cancer cells, as illustrated in Figure 4B. To prove this hypothesis in tumors in living animals, dual fluorescent-labeled micelles were constructed by using BODIPY FL−PEG-*b*-P(Glu)−BODIPY TR (Figure 4C). Intact micelles fluoresce only from the shell-conjugated dye BODIPY FL; the core-conjugated dye BODIPY TR concentrates in the core of the micelles and becomes quenched. As DACHPt is released from the micelles, dequenching of BODIPY TR occurs and the micelles fluoresce increasingly from BODIPY TR. Thus, dual-fluorescent labeling, using both BODIPY FL and BODIPY TR, enables researchers to determine the location of the micelles and the location of drug release that accompanies micelle dissociation (Figure 4C). Observation of the dual fluorescent-labeled micelles by intravital confocal microscopy demonstrates that while DACHPt-loaded micelles circulate stably in the bloodstream even after 12 h (Figure 4D), the micelles

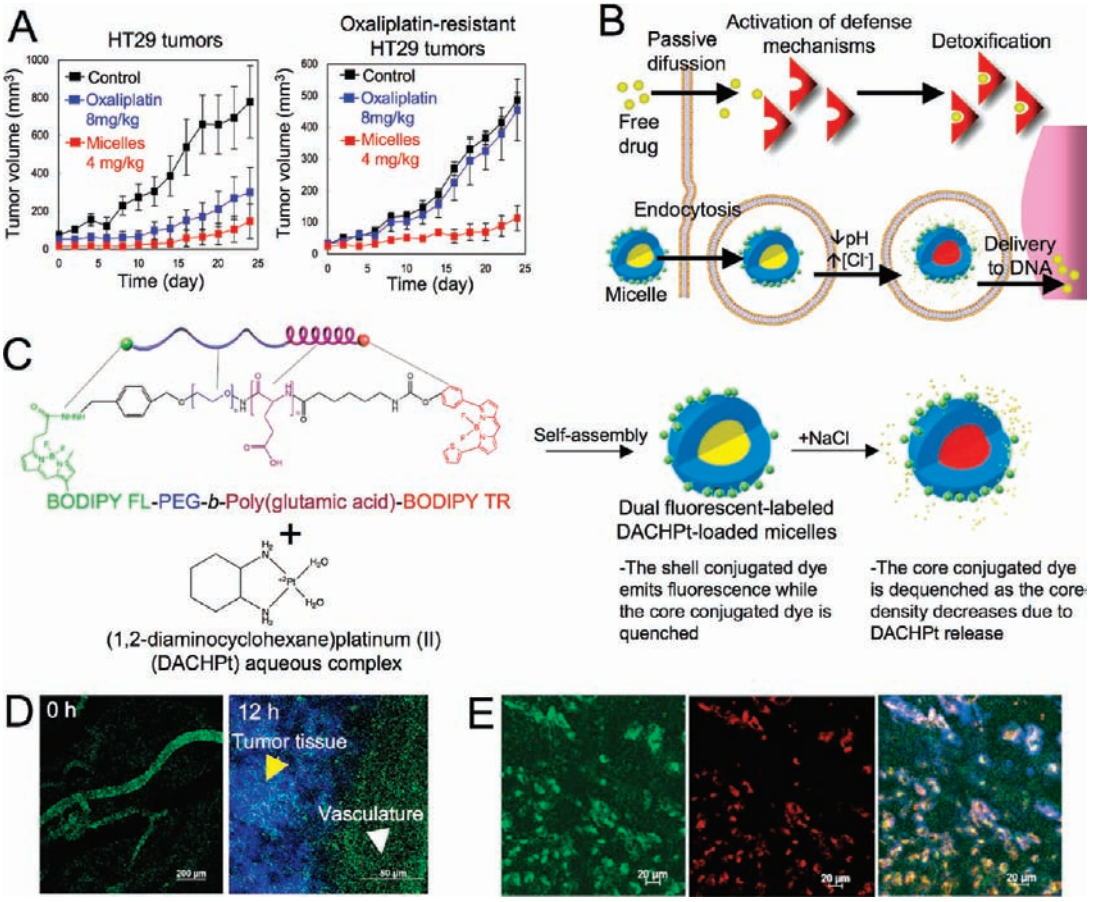

FIGURE 4. Intravital imaging of dual fluorescent-labeled DACHPt-loaded micelles for validation of the concept of intracellular drug delivery in living animals. (A) Antitumor activity of DACHPt-loaded micelles against parent and oxaliplatin-resistant human colon adenocarcinoma HT29 tumor models. The micelles overcame drug resistance in vivo. (B) Proposed mechanism by which DACHPt-loaded micelles overcome drug resistance. (C) Design of dual fluorescent-labeled DACHPt-loaded micelles for visualization of the localization and drug release in the cell. The micelles self-assemble via polymer–metal complex formation between DACHPt and BODIPY FL–poly(ethylene glycol)-*b*-poly(glutamic acid)–BODIPY TR in distilled water. In the micelle state, only BODIPY FL (green) fluoresces and BODIPY TR (red) remains quenched. As DACHPt is released from the micelles in chloride-ion-containing media, BODIPY TR becomes dequenched and begins to fluoresce. (D) In vivo confocal microscopy of micelles in blood vessels and tumor tissue after intravenous administration: immediately after injection and at 12 h after injection. These results suggest that micelles circulate stably in the bloodstream even after 12 h. (E) In vivo confocal microscopy of micelles in tumor tissues at 12 h after injection. Both green and red fluorescence are observed inside the cells, suggesting that the micelles might selectively release DACHPt inside tumor cells. Colors are as follows: green = fluorescence from the shell-conjugated dye BODIPY FL; red = fluorescence from the core-conjugated dye BODIPY TR; blue = fluorescence from the cell membrane (CellMask). Reprinted with permission from ref 33. Copyright 2011 American Association for the Advancement of Science. The merged image on the right shows the colocalization of green and red fluorescence in each cell colored blue, demonstrating subcellular DACHPt delivery by the micellar nanodevice.

penetrate deeply into cancerous tissues after extravasation, internalize into cancer cells distant from the blood vessels, and eventually dissociate and release active drugs selectively in the late endosome of cancer cells (Figure 4E).[33] Thus, the imaging functionality allowed us to validate our hypothesis that DACHPt-loaded micelles can overcome drug resistance through circumvention of the detoxification systems in the cytoplasm.

Further advances in spatial and temporal control of therapeutic effects become possible with external triggering. Externally triggerable nanodevices can enable detection of the target through the contrast-enhanced imaging, followed by pinpoint application of external stimuli to the target site for executing operating functions. Light-triggered nanodevices are attracting increasing attention due to their spatial and temporal control of the therapeutic effects. Moreover, the use of near-infrared lasers and minimally invasive fiber-optic tools facilitates direct targeting of deep tissues. Light has been used to release therapeutic agents from nanodevices[37,38] and to activate agents that produce cytotoxic species.[39] Photodynamic therapy (PDT) is a light-activated treatment modality for various diseases based on the generation of reactive oxygen species (ROS) from photosensitizers by the light irradiation, leading to selective and irreversible destruction of diseased tissues.[39] The generation of heat with light

TABLE 1. Imaging Modalities Used in Theranostic Nanodevices

imaging modality	benefits	limitations	examples of theranostic nanodevices
fluorescence	• easy labeling • great variety of fluorescent molecules and detection wavelengths • good spatial resolution, especially for near-infrared (NIR) light • no ionizing radiation	• clinical application is still limited. • potential incompatibility and toxicity of fluorescent probes • relevant wavelength range limited to 700−900 nm. • limited tissue penetration of light (≤ 2 cm)	Cy 5.5/doxorubicin(DOX) micelles,[22] Cy 5.5/Paclitaxel-loaded micelles[23]
MRI	• high spatial resolution • several contrast agents are widely used for clinical imaging • signal can be enhanced by incorporating contrast agents into nanodevices • no ionizing radiation	• low sensitivity • real-time imaging is difficult • potential toxicity	SPION/DOX micelles,[52−54] Gd-DTPA/(1,2-diaminocyclohexane)platinum(II) (DACHPt)-loaded micelles[51]
PET	• highly sensitive • functional imaging is feasible • signals from radionuclides can be quantified precisely.	• lack of spatial resolution • can give false results if chemical balances within the body are not normal • radionuclides involved have relatively short half-lives • limited accessibility	^{64}Cu/DOX liposomes[59]
SPECT	• highly sensitive • signals from radionuclides can be quantified precisely	• requires use of ionizing radiation • prolonged imaging time • low spatial resolution	^{188}Re/DOX liposomes[60]
CT	• depicts anatomical features precisely	• requires use of ionizing radiation • requires high concentrations of contrast agents • definitive diagnosis is still difficult by CT alone	iodine/DOX liposomes[61]
ultrasound	• safe • low cost • fast and simple	• microbubbles as contrast agents have relatively large size and short blood circulation • destruction of microbubbles ruptures vessel walls and causes hemolysis	microbubbles for gene and drug delivery[62,63]

illumination, that is, photothermal therapy (PTT), also allows localized treatment of diseased tissue by irradiation of photoabsorbers with near-infrared light to cause thermal damage. Nanodevices can improve the accuracy and efficiency of PDT and PTT with minimal damage to normal tissues.[40−42] Moreover, photochemical internalization (PCI), which is a concept of the light-induced cytoplasmic delivery of endocytosed macromolecules based on the photochemical disruption of endosomal membranes,[43] allow nanodevices to activate bioactive molecules such as plasmid DNA, siRNA, and proteins in a light-selective manner.[43−45]

Theranostic Nanodevices: The Emerging Concept of Personalized Nanomedicine

As described in the Introduction, the EPR effect has been widely observed in various tumor models in animals and has become a fundamental principle in carrier-based drug delivery targeted for cancer treatment. Indeed, several formulations such as Doxil and Abraxane are already in clinical use and have been demonstrated to be effective against certain cancers such as Kaposi sarcoma,[8] ovarian cancer,[9] and breast cancer.[10,11] Nevertheless, it remains unclear how effective and different the EPR effect is in different types of cancers in individual patients. For example, pancreatic cancer and diffuse-type gastric cancer (schirrous gastric cancer), which are characterized by less permeable vasculature with pericyte coverage and thick fibrosis, exhibit limited accumulation of macromolecules and particulates and are therefore likely to be intractable by conventional nanoscale carrier systems.[46]

As an approach for drug visualization, direct conjugation of imaging contrast agents to therapeutic entities was found to compromise the biodistribution and biological activity of the therapeutic entity. In contrast, integration of imaging functionality into nanoscale drug carriers does not affect

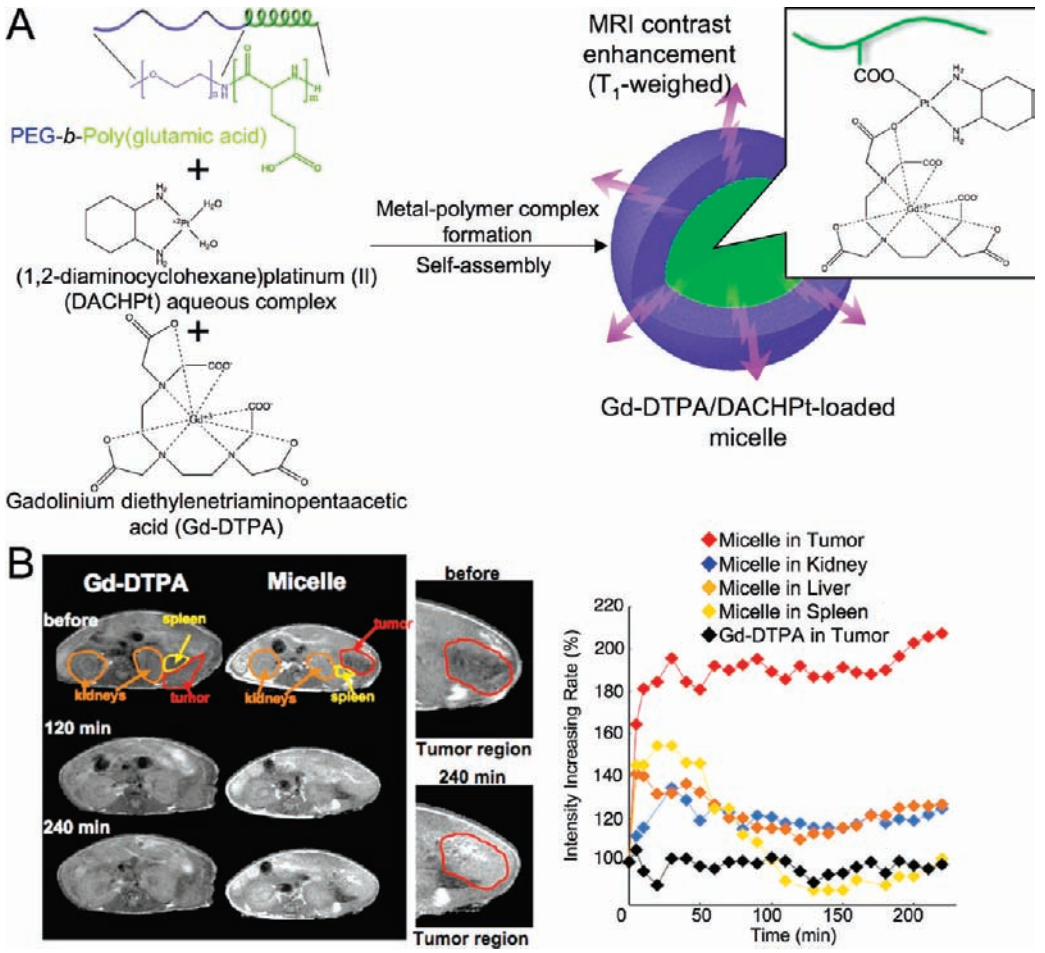

FIGURE 5. Gd–DTPA/DACHPt-loaded micelles for tracking biodistribution and therapeutic effects. (A) Scheme of Gd–DTPA/DACHPt-loaded micelles formation. Micelles self-assemble by metal-complex formation between DACHPt and the carboxylic groups of poly(glutamic acid) in PEG-*b*-P(Glu). (B) MRI of orthotopic pancreatic tumor bearing mice after intravenous injection of the clinically approved MRI contrast agent, Gd–DTPA, or Gd–DTPA/DACHPt-loaded micelles. The micelles specifically enhance the signal at the tumor site for a prolonged time. Reprinted with permission from ref 51. Copyright 2010 American Association for Cancer Research.

biodistribution and biological activity and thus offers a promising theranostic platform. Almost all imaging modalities have been used in theranostic nanodevices, and imaging has successfully provided information about anatomic distribution, pharmacokinetics, and pharmacodynamics of nanodevices and delivered drugs (Table 1). Among these imaging modalities, MRI is particularly advantageous because it offers good spatial resolution in the entire body and good contrast among soft tissues, making it especially useful for imaging muscle, brain, heart, and tumors. The basis for a MRI signal is the precession of water hydrogen nuclei in an applied magnetic field and MRI contrast agents can be used to shorten the relaxation times of water (spin–lattice relaxation time T_1 and spin–spin relaxation time T_2); contrast agents with higher relaxivities [r_1 (= $1/T_1$) and r_2 (= $1/T_2$)] give stronger contrast enhancement.[47] Paramagnetic molecules such as gadolinium (Gd) and manganese (Mn) for T_1-weighted MRI[48–51] and superparamagnetic contrast agents such as iron-oxide nanoparticles for T_2-weighted MRI[52–54] have been incorporated into nanodevices to enable tracing of tissue distribution.

Regarding T_1-enhanced contrast agents, their relaxivity is influenced by numerous parameters. Efforts to increase the relaxivity of Gd contrast agents have focused on three approaches: increasing the hydration number, optimizing the water-exchange rate, and slowing molecular reorientation.[47] However, increasing the hydration number of Gd complexes reduces their plasma stability, and optimizing the water-exchange rate requires direct engineering on the Gd complex; hence, the most practical of these approaches is to slow molecular reorientation.

One strategy to slow molecular reorientation is to decrease the mobility of Gd complexes by incorporating them into micelles, thus forming supramolecular structures with increased relaxivities.[48–50] We recently incorporated

gadolinium–diethylenetriaminepentaacetic acid (Gd–DTPA), a clinically approved T_1-weighted MRI contrast agent into DACHPt-loaded micelles by utilizing the reversible complex formation between DACHPt and Gd–DTPA (Figure 5A).[51] Incorporation of Gd–DTPA into the micellar core increases longitudinal relaxivity r_1 from 3.5 to 80.5 mmol L^{-1} s^{-1}. Gd–DTPA/DACHPt-loaded micelles released less toxic Gd–DTPA under a physiological condition, followed by its rapid renal clearance, avoiding problems of toxicity caused by long-term accumulation of Gd^{3+} ions in the body. In animal experiments, Gd–DTPA/DACHPt-loaded micelles accumulated effectively in subcutaneous murine colon carcinoma and orthotopic human pancreatic adenocarcinoma models, enabling successful contrast-enhanced MR imaging of those tumors (Figure 5B). In addition to real-time observation of tumor accumulation, contrast-enhanced MRI using Gd–DTPA/DACHPt-loaded micelles also enables the measurement of the volume of orthotopic pancreatic tumors in the abdominal cavity and, thus, noninvasive evaluation of their enhanced antitumor activity compared with free oxaliplatin. Because clinical chemotherapy regimens are given in periodic cycles over weeks or months, monitoring of tumor size by MRI using Gd–DTPA/DACHPt-loaded micelles is clinically feasible.

Regarding T_2-enhanced contrast agents, aggregation of magnetic nanoparticles dephases the spins of neighboring water protons efficiently, enhancing the net rate r_2 of transverse relaxation. The value of T_2 for a magnetic nanoparticle is inversely proportional to its cross-sectional area, so the same amount of magnetized material is more effective when dispersed as fewer large aggregates than as more smaller aggregates.[55] Accordingly, clustering superparamagnetic iron-oxide nanoparticles (SPIONs) inside polymeric micelles prepared from poly(ethylene glycol)-*block*-poly(D,L-lactide) augments their relaxivity.[52] Relaxivity enhancement of PEGylated SPIONs incorporating Dox was critical for the evaluation of their tumor accumulation by MRI.[53,54]

At present, therapeutic strategies are evaluated through population-based studies or randomized clinical trials, neither of which considers individual differences among patients. In contrast, theranostic nanodevices may enable the evaluation of real-time therapeutic responses in individual patients. They may also facilitate evaluation by enabling medical clinicians to monitor pharmacokinetic and therapeutic responses, perhaps in lieu of detecting traditional end points such as tumor shrinkage. Furthermore, theranostic nanodevices with integrated functional imaging may provide pinpoint information regarding cellular responses and biomarker expression within diseased tissues, which can be used in combination with current serum biomarkers. Nevertheless, for theranostic nanodevices to be deemed suitable for clinical use, designers must surmount the challenges involving formulation toxicity, stability under in vivo conditions, inconsistencies in the clearance rates of imaging and therapeutic agents, optimization of the dosage needed for therapy and diagnosis, and, of course, regulatory definition and acceptance. If these challenges can be surmounted, this emerging approach will likely become a safe and efficient strategy for disease management.

Prospects for the Future

Nanodevices must grow substantially in sophistication before we can experience focused smart nanomedicines in which a single platform executes seamless processes ranging from ultrasensitive diagnosis to pinpoint therapy. Integration of the imaging function into nanodevice designs provides tools for assessing nanodevice biodistribution and other functions. To date, nanodevices have been mostly applied to diagnosis and treatment of cancers, because they can selectively and effectively accumulate in cancerous tissues due to the EPR effect. For further applications of nanodevices to organs and tissues other than cancer, nanodevices need to be equipped with the capabilities to overcome several biological barriers, including extravasation, tissue penetration, and cellular internalization at the target site. Especially, the extravasation in specific tissues should be the first critical barrier. In this regard, recent advances in in vivo phage-display techniques have led to the discovery of peptides specific to the vascular endothelium in particular organs and tissues (vascular mapping),[56] motivating researchers to develop nanodevices that actively target specific peptides. Targeting vascular endothelium can increase nanodevice accumulation at the target site (tissue-specific delivery) and also facilitate nanodevice transport across the vascular wall (transcytosis), even in tissues where the EPR effect does not operate to cause accumulation.[57,58] Actively targetable nanodevices can potentially overcome other formidable biological barriers as well, such as the blood-brain barrier. Among promising directions of investigation, nanodevices will eventually permit in situ detection and manipulation of the expression of specific molecules, molecular interactions, and reactions, providing new tools for the direct study of molecular and cellular biological events in living animals. Such sophisticated nanodevices

should be useful for drug discovery and development based on validation of molecular targets by whole-body imaging.

Medical nanodevices will continue to evolve by capitalizing on advances in related fields such as drug delivery, materials science, molecular imaging, molecular and cellular biology, and clinical oncology, as well as on technical improvements for assessment of nanodevices. Multidisciplinary approaches resulting from collaborations among researchers from various fields are clearly indispensable to this evolution and the realization of innovative nanodevices.

BIOGRAPHICAL INFORMATION

Horacio Cabral received his Ph.D. under the supervision of Prof. K. Kataoka in Materials Engineering from the University of Tokyo in 2007. He worked as an assistant professor at the Division of Clinical Biotechnology, Graduate School of Medicine, the University of Tokyo until 2009. Since 2010, he has been an associate professor at the Department of Bioengineering, the University of Tokyo. His main research interests relate to smart nanodevices for the diagnosis and therapy of cancer.

Nobuhiro Nishiyama received his Ph.D. under the supervision of Prof. K. Kataoka in Materials Engineering from the University of Tokyo in 2001. After a postdoctoral fellowship in the research group of Professor J. Kopecek at the University of Utah, he joined in the research group of Prof. K. Kataoka again in 2003 and has been an associate professor in the Division of Clinical Biotechnology, Graduate School of Medicine, the University of Tokyo since 2009. His main interest concerns the biomedical applications of intelligent nanodevices for drug and gene delivery.

Kazunori Kataoka received his Ph.D. from the University of Tokyo in 1979. He has been a professor of Biomaterials at Graduate School of Engineering, the University of Tokyo, Japan since 1998. He has also been appointed a joint position since 2004 from Graduate School of Medicine, the University of Tokyo as a professor of Clinical Biotechnology. Dr. Kataoka is the author of more than 380 scientific papers in international journals and is on the board of 14 internationally renowned scientific journals. His current major research interests include the development of new polymeric carrier systems, especially block copolymer micelles, for drug and gene targeting.

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FOOTNOTES

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