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In Vivo Targeted Delivery of Nanoparticles for Theranosis

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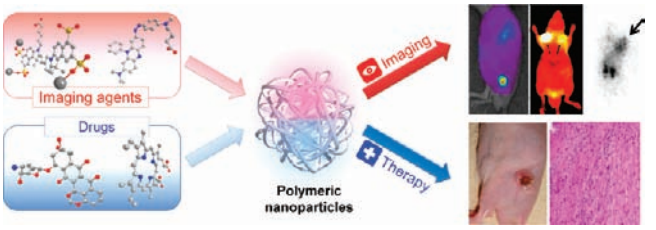

Therapy and diagnosis are two major categories in the clinical treatment of disease. Recently, the word "theranosis" has been created, combining the words to describe the implementation of these two distinct pursuits simultaneously. For successful theranosis, the efficient delivery of imaging agents and drugs is critical to provide sufficient imaging signal or drug concentration in the targeted disease site. To achieve this purpose, biomedical researchers have developed various nanoparticles composed of organic or inorganic materials. However, the targeted delivery of these nanoparticles in animal models and patients remains a difficult hurdle for many researchers, even if they show useful properties in cell culture condition.

In this Account, we review our strategies for developing theranostic nanopartides to accomplish in vivo targeted delivery of imaging agents and drugs. By applying these rational strategies, we achieved fine multimodal imaging and successful therapy. Our first strategy involves physicochemical optimization of nanoparticles for long circulation and an enhanced permeation and retention (EPR) effect. We accomplished this result by testing various materials in mouse models and optimizing the physical properties of the materials with imaging techniques. Through these experiments, we developed a glycol chitosan nanoparticle (CNP), which is suitable for angiogenic diseases, such as cancers, even without an additional targeting moiety. The in vivo mechanism of this particle was examined through rationally designed experiments. In addition, we evaluated and compared the biodistribution and target-site accumulation of bare and drug-loaded nanoparticles.

We then focus on the targeting moieties that bind to cell surface receptors. Small peptides were selected as targeting moieties because of their stability, low cost, size, and activity per unit mass. Through phage display screening, the interleukin-4 receptor binding peptide was discovered, and we combined it with our nanoparticles. This product accumulated efficiently in atherosclerotic regions or tumors during both imaging and therapy. We also developed hyaluronic acid nanoparticles that can bind efficiently to the CD44 antigen receptors abundant in many tumor cells. Their delivery mechanism is based on both physicochemical optimization for the EPR effect and receptor-mediated endocytosis by their hyaluronic acid backbone.

Finally, we introduce the stimuli-responsive system related to the chemical and biological changes in the target disease site. Considering the relatively low pH in tumors and ischemic sites, we applied pH-sensitive micelle to optical imaging, magnetic resonance imaging, anticancer drug delivery, and photodynamic therapy. In addition, we successfully evaluated the in vivo imaging of enzyme activity at the target site with an enzyme-specific peptide sequence and CNPs.

On the basis of these strategies, we were able to develop self-assembled nanoparticles for in vivo targeted delivery, and successful results were obtained with them in animal models for both imaging and therapy. We anticipate that these rational strategies, as well as our nanoparticles, will be applied in both the diagnosis and therapy of many human diseases. These theranostic nanoparticles are expected to greatly contribute to optimized therapy for individual patients as personalized medicine, in the near future.

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1. Introduction

The word "theranosis" was coined to describe the current biomedical efforts to combine diagnostic and therapeutic modalities by one unified material and to develop individually designed therapies against various diseases to accomplish personalized medicine.[1] The need for personalized medicine arose from the consensus that many diseases like cancer are originally heterogeneous, and thus clinical treatments should reflect patient characteristics and stages of disease progression.[2] Large numbers of current researchers hope and expect that a combination of diagnosis and therapy can produce rationally organized clinical treatments that are optimal for each patient.[3]

In both diagnosis and therapy, one of the most essential requirements is efficient delivery of imaging agents and drugs to the target site. For precise diagnosis of disease, many imaging modalities such as fluorescence optical imaging, magnetic resonance imaging (MRI), positron-emission tomography (PET), and computed tomography (CT) have been developed and used in biomedical fields.[4] To investigate the disease site using one of these modalities, the intensity of the imaging signals should be higher in the target site than in the surrounding area. Various imaging agents have been developed for this purpose, and they require efficient delivery to the target site.[5] In the case of drug delivery, many treatments will not provide favorable clinical outcomes if the drug concentration in the target disease site is not sufficient to generate therapeutic efficacy.[6] Moreover, in many cases, a large amount of the administrated drug is also delivered to normal tissues, which could result in the severe side effects that patients often experience.[7] Therefore, an essential approach to overcome this crucial obstacle is the development of optimized and targeted delivery systems for imaging agents or drugs.[8]

For this purpose, a variety of nanoparticles have been developed using various organic or inorganic materials and used widely for imaging and drug delivery.[9−11] Consequently, a precise description of their base materials or applications has been reviewed in many recent papers.[12] However, in vivo targeted delivery still remains the key limiting factor for many nanoparticles that exhibit useful properties in cell culture systems.[13,14] Therefore, this Account focuses mainly on our own efforts and strategies to develop theranostic nanoparticles that enable target-specific delivery of imaging agents and drugs for in vivo systems. Especially, we described in this Account mainly polymeric nanoparticles that have amphiphilic characters enabling self-assembly in aqueous conditions. Imaging agents or drugs can be introduced easily into them by loading or conjugation. Inorganic nanoparticles and carbon nanotubes for theranosis were reviewed in recent papers by other researchers.[1,15]

2. Physicochemical Optimization of Nanoparticles for Intravenous Injection

Nanoparticles are particularly advantageous for intravenous injection, because their nanosize has special meaning in this condition.[9] When intravenously injected, particles smaller than 5 nm are removed from blood by rapid renal clearance through kidney, whereas large microsized particles are filtrated mechanically by sinusoids and cleared by the reticuloendothelial system (RES) of liver and spleen.[16] Therefore, nanoparticles with 10−500 nm sizes can remain in the circulation for an extended period of time when injected intravenously and can be employed in rational strategies for targeted delivery, like passive or active targeting.[17]

2.1. Enhanced Permeation and Retention (EPR) Effect and Glycol Chitosan Nanoparticle (CNP). Because of the rapid construction of new, fenestrated vascular structures, tumors are more readily permeable than normal tissues to nanoparticles.[14] This phenomenon has been identified as the EPR effect and its fundamental mechanism is exploited for passive targeting of nanoparticles to solid tumors.[18] And this EPR effect also can be observed in other angiogenic disease like arthritis.[19] Although many studies on nanoparticles have been performed on the basis of the EPR effects, their in vivo data have revealed that the tumor specificity of the nanoparticles was only slightly improved compared with the controls in many cases.[16]

Among various nanoparticles, our glycol chitosan nanoparticle (CNP) was superior in tumor-targeted delivery during many in vivo experiments.[20−22] In our recent paper, its tumor targeting ability was evaluated precisely in tumor-bearing mice by using the near-infrared fluorescent (NIRF) dye, Cy5.5, and noninvasive fluorescence imaging (Figure 1).[23] CNP was synthesized by conjugating hydrophilic glycol chitosan and hydrophobic cholanic acid, and this combination allowed the self-assembly into nanoparticles in aqueous conditions. It is about 260 nm in size, and gel filtration data revealed that its deformability is higher than that of polystyrene beads of similar size. We believe this deformability may play a pivotal role in its extended duration in circulation and its accumulation in the tumor, because its size is larger than the traditional, optimal size for EPR effect.[13,14] When two differently sized SCC7 tumors were established in mice and Cy5.5−GC nanoparticles were

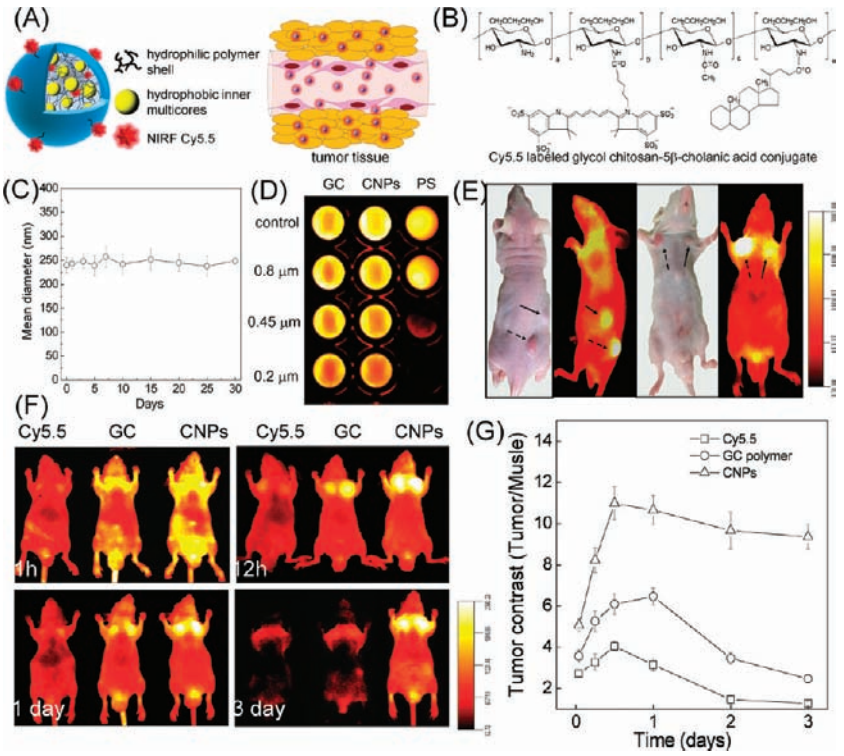

FIGURE 1. Glycol chitosan nanoparticle (CNP) and tumor targeting based on EPR effect. (A) Schematic illustration of self-assembled CNP and EPR effect in tumor tissue. (B) Chemical structure of Cy5.5-labeled glycol chitosan−cholanic acid conjugate. (C) Time-dependent size determination of CNP in PBS. (D) Filtration test of glycol chitosan polymer, CNP, and polystyrene beads with different pore sizes. (E) In vivo imaging of Cy5.5−CNPs in mice with different size of SCC7 tumors (2.6 ± 0.3 mm (solid arrow) and 6.2 ± 0.5 mm (dotted arrow)). (F) Time-dependent NIRF images of free Cy5.5, Cy5.5−glycol chitosan polymers, and Cy5.5−CNPs in SCC7 tumor-bearing mice. (G) Tumor to background (muscle) fluorescence ratio in panel F as a function of time.

injected via the tail vein, both tumors were significantly delineated from the surrounding normal tissue. However, the NIRF signal was proportional to the tumor size, demonstrating that the tumor targeting mechanism of CNP is based on the EPR effect related to rapid tumor growth. Strong NIRF signal was detected for 3 days in tumors of mice treated with CNPs, unlike the case of Cy5.5 or GC polymer. This finding proved the extended circulation time and tumor-targeted delivery of CNPs.

2.2. Optimization of CNPs. Many factors like size and charge should be considered to accomplish targeted delivery of nanoparticles.[14] To select an adequate polymer for nanoparticles, we synthesized several self-assembled nanoparticles with different polymer backbones and investigated their biodistribution in tumor-bearing mice.[24] The scintigraphic images of CNPs revealed clear delineation of the tumor against surrounding tissues, showing the superior efficiency of CNPs in tumor targeting. In contrast, gelatin or heparin nanoparticles were washed rapidly out of the blood circulation. Poly(ethylene glycol) (PEG)−gelatin nanoparticles remained in the blood flow for a longer duration but accumulated poorly in tumor. Moreover, three glycol chitosan polymers with different molecular weights (20, 100, and 250 kDa) were modified with cholanic acid at same molar ratio and tested in mice to evaluate molecular weight effect of polymer backbone.[25] The results suggested that CNPs containing 250 kDa glycol chitosan have increased blood circulation time, which allows for enhanced tumor targeting.

Another type of optimization studies for CNP was described in a recent paper. In collaboration with Kim group, we evaluated the in vivo biodistribution and tumor site accumulation of CNPs with or without drug by using radioisotope imaging (Figure 2).[26] Two different amounts (3.3% for CNP1 and 7.8% for CNP3) of *N*-acetyl histidine (NAcHis) were conjugated to glycol chitosan as a hydrophobic moiety, and their biodistribution in tumor-bearing mice was evaluated with ^{131}I. Moreover, we further observed the biodistribution of doxorubicin, which is loaded in these two CNPs. Our tumor suppression data showed that the therapeutic efficacy of nanoparticles is dependent on the distribution of drugs, and it may differ from the distribution of bare nanoparticles. This evidence

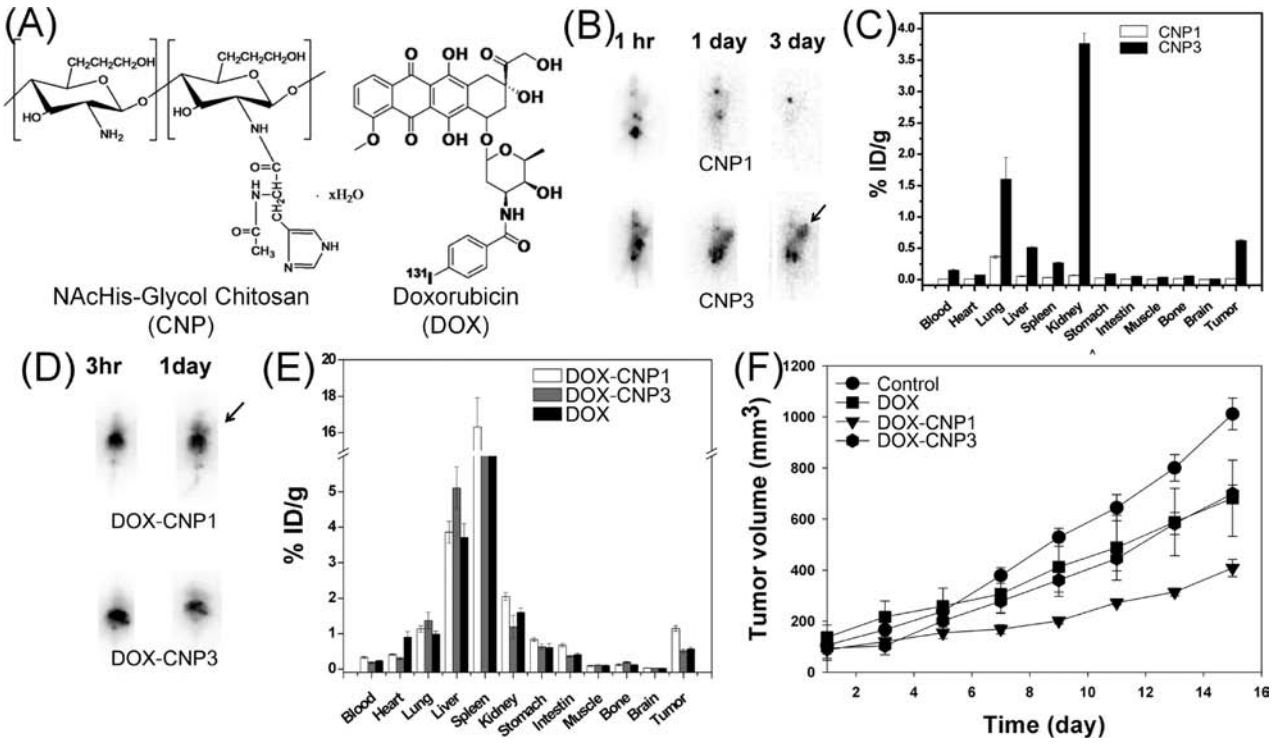

FIGURE 2. Optimization of CNPs with or without drug by radionuclide imaging. (A) Chemical structures of *N*-acetyl histidine modified glycol chitosan polymer and isotope-labeled doxorubicin. (B) Scintigraphic images of HT29 tumor-bearing mice after i.v. injection of ^{131}I-labeled CNPs. The tumor site was indicated with black arrow in animal. (C) Tissue distributions of ^{131}I-labeled CNPs after i.v. injection of nanoparticles. (D) Scintigraphic images of HT29 tumor bearing mice after i.v. injection of ^{131}I-labeled DOX-loaded CNPs. The tumor site was indicated with black arrow in animal. (E) Tissue distributions of ^{131}I-labeled DOX loaded CNPs (F) Antitumor effect of DOX-CNPs in HT29 tumor bearing mice.

demonstrates that the drug-loading process may highly affect the physicochemical characteristics of nanoparticles and alter their in vivo distribution. Moreover, we found that real-time molecular imaging is useful for optimization of nanoparticles.[4]

3. Cell Surface Receptors and Target-Cell-Specific Delivery of Nanoparticles

Most cells express a large number of receptors on their surfaces, and the types of receptors vary widely in different types of cell lines. Consequently, the conjugation of nanoparticles with receptor-binding molecules can selectively increase the adherence or uptake of nanoparticles to target cells.[7] For this purpose, various targeting molecules such as antibodies, antibody fragments, peptides, and DNA/RNA aptamers have been applied to nanoparticles for theranosis.[7,27] However, care must be taken to ensure that these targeting molecules cannot always guarantee the excessively increased accumulation of nanoparticles in the target organ or tissues but only can increase the internalization of the nanoparticles by the target cells.[13,28,29] According to many recent papers, the pharmacokinetics and biodistribution of nanoparticles are largely dependent on their physicochemical characters; thus these factors should be considered simultaneously even if targeting molecules are used.[13]

3.1. Atherosclerotic Plaque-Homing Peptide-Conjugated Nanoparticles Targeting the Interleukin (IL)-4 Receptor. Peptides have several advantages over antibodies in their use as targeting molecules for nanoparticles. For example, their manufacturing cost is low, and they have higher activity per unit. They are also stable, enabling long-term storage and easy handling. Furthermore, the associated risk of unintended effects on the host immune system is low, and their small size is less likely to change the optimized physicochemical properties of nanoparticles.[30]

In a previous paper, an atherosclerotic plaque-homing peptide (CRKRLDRNC; AP peptide) was discovered by phage display screening. The peptide could adhere to atherosclerotic plaque by binding the interleukin (IL)-4 receptors on macrophages, endothelial cells, and smooth muscle cells.[31] In collaboration with Lee group, we developed an efficient imaging probe for in vivo fluorescence imaging of the atherosclerotic lesion by conjugating the AP peptide and Cy5.5 to CNP (Figure 3).[32] The conjugated CNPs demonstrated a higher

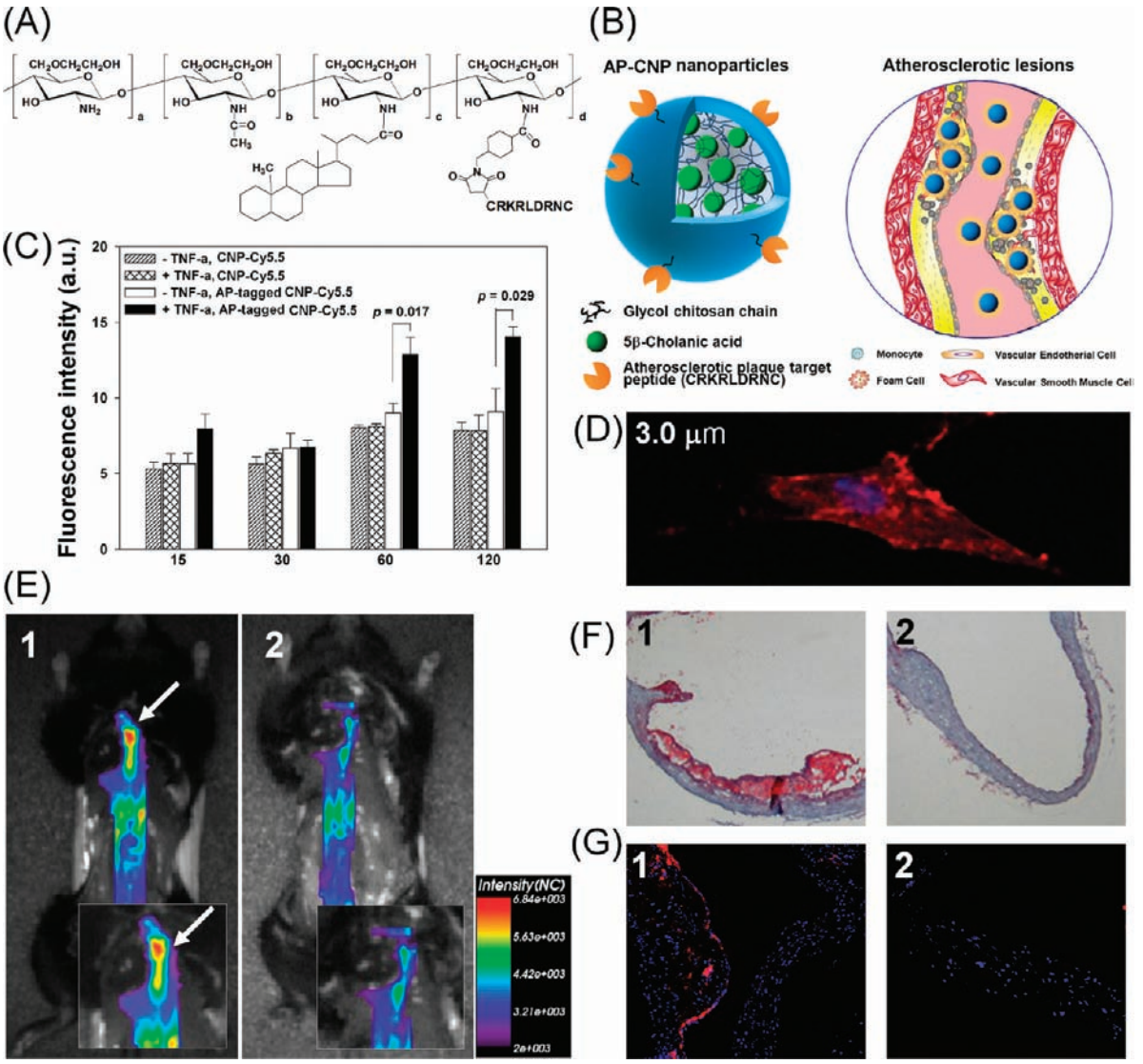

FIGURE 3. AP peptide conjugated CNP for IL-4 receptor targeting and in vivo NIRF imaging of atherosclerotic plaque. (A) Chemical structure of atherosclerotic plaque-targeting peptide (CRKRLDRNC, AP) conjugated CNP. (B) Illustration of AP−CNPs and their in vivo targeting to atherosclerotic lesions. (C) Time-dependent fluorospectrometric study to evaluate the binding characteristics of bare and AP−CNPs to unactivated and TNF-α-activated BAECs. (D) Serial fluorescence Z-section image of activated BAECs bound to AP−CNPs showing that most nanoparticles bound to the membrane of cells. (E) The NIRF image of the exposed aorta in an Ldlr−/− mouse (1) and in a normal mouse (2) after i.v. injection of AP−CNPs. (F) Oil Red O lipid staining of aortas in an Ldlr−/− mouse (1) and in a normal mouse (2). (G) NIRF microscopy of aortas in an Ldlr−/− mouse (1) and in a normal mouse (2) after i.v. injection of AP−CNPs.

binding affinity to tumor necrosis factor (TNF)-α-activated bovine aortic endothelial cells (BAECs) than to nonactivated BAECs. In vivo NIRF imaging data revealed larger amounts of these AP−Cy5.5−CNPs bound to atherosclerotic lesions in the atherosclerotic mouse which lacks the low-density lipoprotein receptor (Ldlr−/−), than to the same lesions in a normal mouse. These results may be because of the combinatory effect of the long circulation by CNPs and the adherence to atherosclerotic lesion by AP peptide. In addition, the AP peptide carries great potential for tumor-targeted nanoparticles, because IL-4 receptors are abundant in many cancers.[33] In another paper, we proved this potential of AP peptide by conjugation with pH-sensitive micelles and eliciting successful chemotherapy with doxorubicin in the breast cancer mouse model.[34]

3.2. Hyaluronic Acid (HA) Nanoparticles Targeting the CD44 Receptor. Hyaluronic acid (HA) is an anionic polysaccharide and is one of the most abundant polysaccharides in human and animals.[35] Because of biocompatibility and low cost, it has received much attention for application in biomedical fields.[36,37] Importantly, the use of HA as a targeting moiety for cancer therapy has been investigated by many

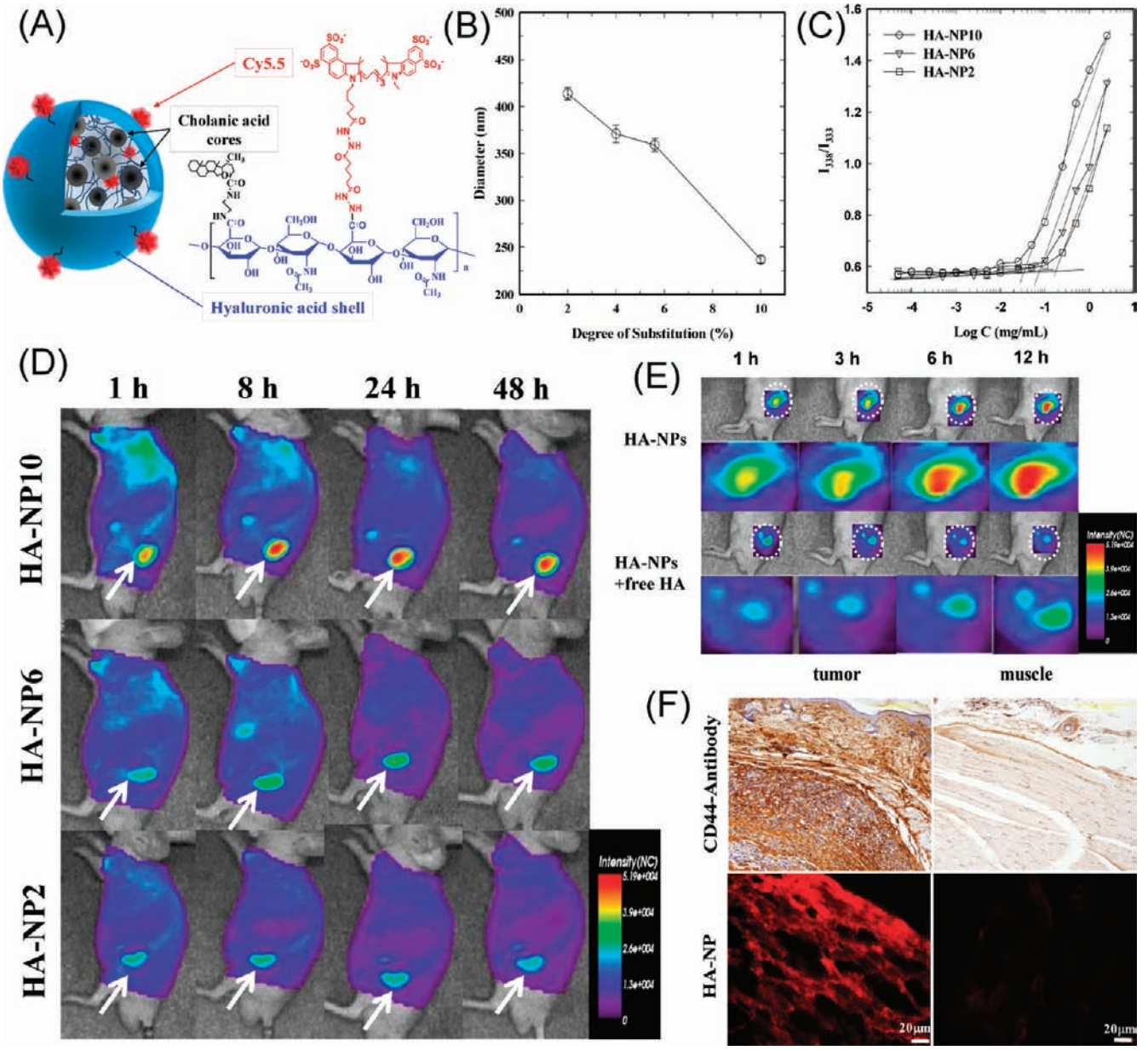

FIGURE 4. Hyaluronic acid nanoparticle with optimized nanostructure and CD44 receptor-binding activity for tumor targeting. (A) Illustration and chemical structure of Cy5.5-conjugated HA nanoparticle. (B) Particle size of HA nanoparticles with different amounts of conjugated cholanic acid. (C) Particle stability of HA nanoparticles based on intensity ratio (I_{338}/I_{333}) from pyrene excitation spectra. The number after HA-NP indicates the degree of substitution of cholanic acid. (D) Time-dependent NIRF images of SCC7 tumor-bearing mice after i.v. injection of HA nanoparticles. (E) In vivo fluorescence images of HA nanoparticles in tumors with and without preinjection of free-HA. (F) Optical microscopy images of tumor and muscle tissues stained with CD44 antibody (upper) and NIRF microscopy images (lower) at two days postinjection of HA nanoparticles.

researchers because the HA receptor CD44 is overexpressed in various cancer cells.[38]

In a recent study, we synthesized amphiphilic HA conjugates by conjugating hydrophobic cholanic acid and hydrophilic HA in collaboration with Park group.[39] The resulting HA conjugates could self-assemble into stable nanoparticles in aqueous solution, as in the case of GC nanoparticles, and was expected to efficiently contain and deliver the drugs or imaging agents.

The in vivo targeting mechanism of HA nanoparticles to the tumor site is evaluated in another paper (Figure 4).[40] HA can be used not only as the stable hydrophilic shell of nanoparticles but also as the targeting moiety that binds to receptors on tumor cells. However, the in vivo tumor-targeting efficiency of HA nanoparticles was significantly dependent on the quantity of hydrophobic cholanic acid. This result demonstrates that stable nanoparticles are advantageous for targeting tumors,

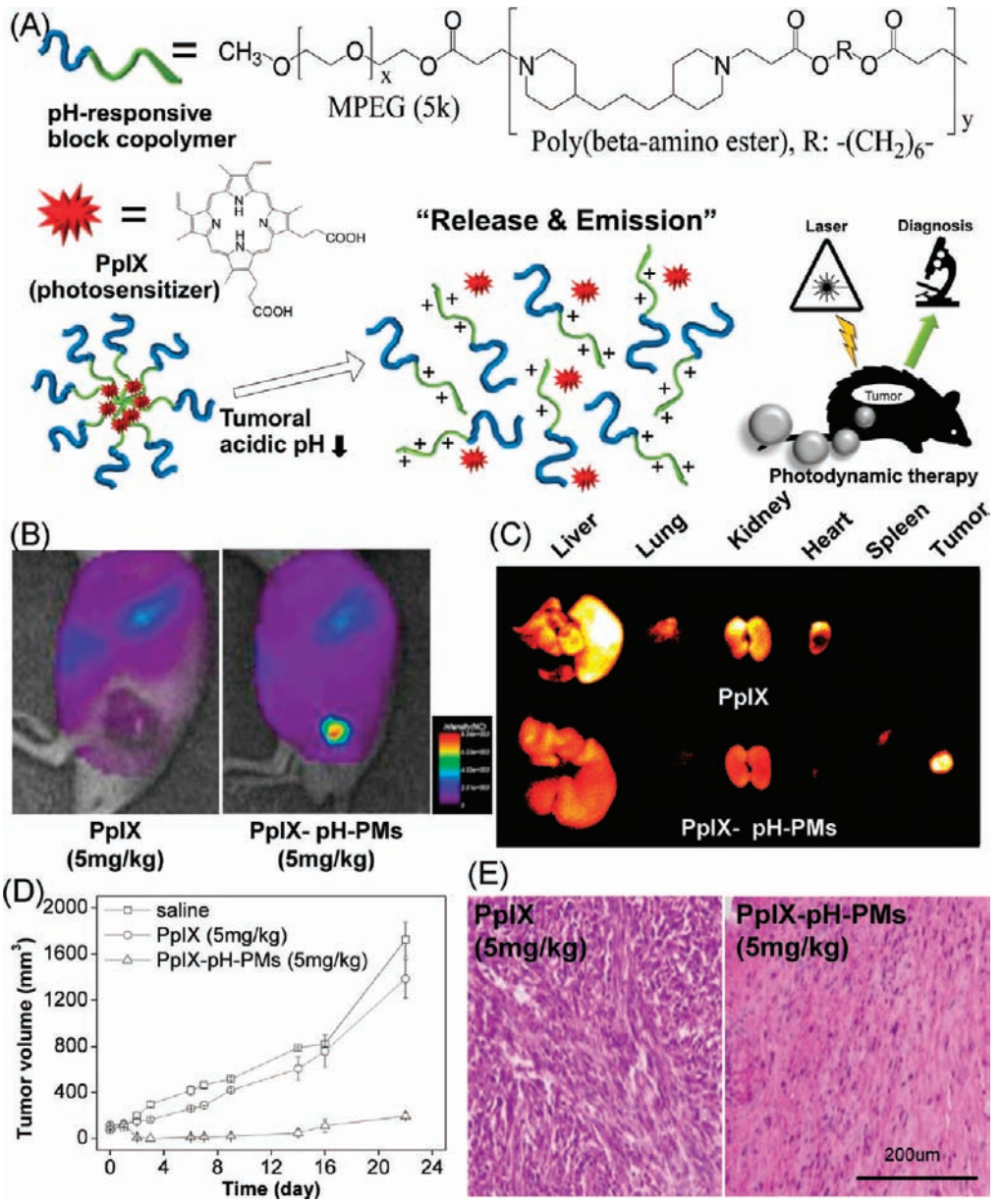

FIGURE 5. Acidic pH-sensitive polymeric micelle and simultaneous in vivo tumor imaging and photodynamic therapy. (A) Schematic diagram of tumoral pH-responsive photosensitizer release from pH-sensitive micelle and in vivo tumor imaging/therapy. (B) High accumulation of photosensitizer in SCC7 tumor-bearing mice after injection of PpIX-loaded pH-sensitive micelle. (C) Ex vivo organ distribution of PpIX in panel B. (D) In vivo photodynamic tumor therapy with pH-sensitive micelle and PpIX. (E) H&E staining of SCC7 tumor tissues from panel D.

and prolonged circulation is required for sufficient binding to target cell receptors. In addition, we have shown that the physicochemically optimized nanostructure and receptor targeting moiety can be simultaneously created with only two components, HA and hydrophobic cholanic acid.

4. Chemical and Biological Environment of Target Site and Stimuli-Responsive Delivery

Many chemical or biological changes in the microenvironment are generated in the human body during disease or inflammation. Typical changes indicating an abnormal state include temperature, pH, enzyme levels, and oxygen concentration. These particular properties of the disease site have been investigated extensively to understand the mechanisms of disease and develop diagnostic methods or drugs.[41,42] Interestingly, such information is also highly valuable for the development of theranostic nanoparticles, which can be designed to detect these stimuli and release drugs or imaging agent at target disease site.[43,44]

4.1. pH-Sensitive Micelle for Tumor and Ischemic Region Targeting. Acidic pH microenvironment is an unstable

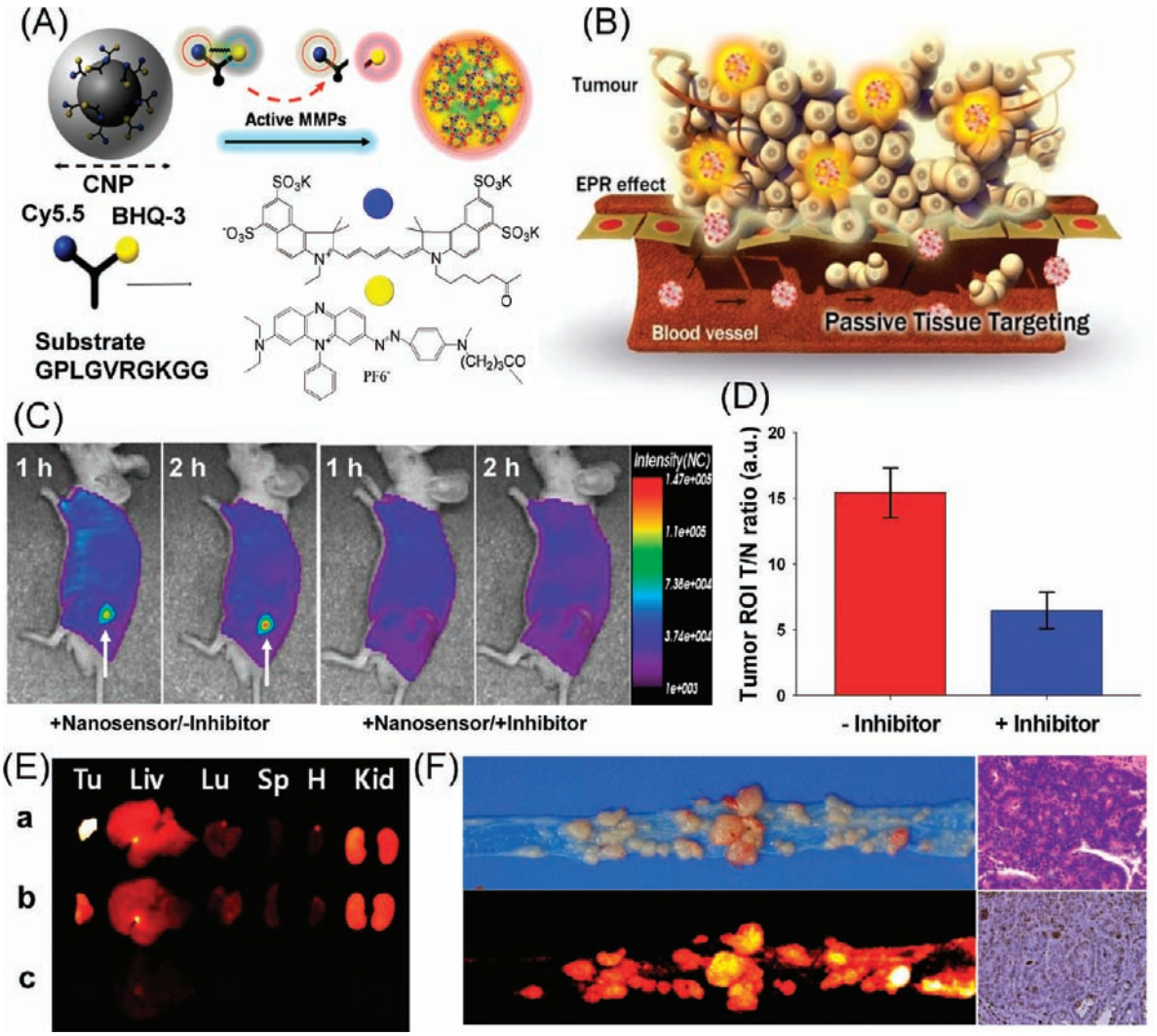

FIGURE 6. Enzyme-responsive probes with quenched cleavable peptide conjugated CNP and in vivo matrix metalloproteinase (MMP) imaging in tumors. (A) Design concept of MMP enzyme-responsive fluorescence probes based on cleavable peptide and CNP. (B) Passive tumor targeting and MMP-responsive NIRF imaging of nanoparticle probe. (C) In vivo NIRF imaging of MMP enzymes in SCC7 flank tumor model using nanoparticle probe. (D) NIRF signals of tumor tissues from panel C with and without inhibitor. (E) Ex vivo NIRF tumor and organ images of mice injected with nanoparticle probes (Tu, tumor; Liv, liver; Lu, lung; Sp, spleen; H, heart; Kid, kidney). Nanoparticle probe-treated animals without (a) and with (b) the inhibitor, and saline-treated animals (c). (F) Photo images and imunohistological analysis of colon cancers from mice injected with nanoparticle probes.

state of pH homeostasis that can originate from ischemia, inflammation, wound healing, infection, and cancer.[45,46] The extracellular pH in most tumor tissues is lower than that in normal tissue because of insufficient vascular formation and increased glycolysis.[47] A similar acidic pH related to neuronal cell injury has also been observed in brain tissue affected by ischemic stroke.[48]

In a recent paper, we used a pH-sensitive polymeric micelle as an in vivo targeted delivery system to the acidic site in collaboration with Lee group.[49] The micelle is composed of hydrophilic poly(ethylene glycol) (PEG) and pH-sensitive poly(amino ester) (PAE), and it self-assembles into a stable micelle that can carry drugs or imaging agents at a normal pH (>7). However, the micelle exhibits pH-sensitive disruption at acidic pH because the tertiary amine groups in the hydrophobic PAE block protons and become hydrophilic. Initially, this micelle was designed for tumor-targeted drug delivery, and in vivo tumor suppression experiments with doxorubicin and camptothecin have proven the success of this goal.[49] Moreover, this micelle has been shown to enable noninvasive in vivo fluorescence imaging of the tumor site and MRI of brain ischemia.[50,51] For photodynamic therapy, tumor-targeted delivery of hydrophobic photosensitizers with this micelle resulted in simultaneous tumor diagnosis and therapy based on the fluorescence and singlet oxygen from photosensitizers (Figure 5).[52]

4.2. Enzyme-Responsive Peptide-Based Nanoparticles. Enzymes play an essential role in many biomedical processes like metastasis and angiogenesis of tumor tissue and degradation of the extracellular matrix in arthritis.[53] At the disease site, certain enzymes are overexpressed at particular stages of the disease, and many researchers have investigated these enzymes as targets of diagnosis and therapy.[54] Among these enzymes, a large number have proteolytic activity and cleave specific peptide sequences from proteins that are critical in many mechanisms of disease or immune defense.[55] Knowledge of specific peptide sequences and degradation can be applied usefully to achieve enzyme-responsive release of imaging agents or drugs.[56,57]

Matrix metalloproteinases (MMPs) play a role in certain inflammatory diseases and cancer progression and are therefore potentially useful for imaging or drug delivery to target sites in diseases like arthritis or cancer.[58] In a recent study, we developed NIRF nanoprobes composed of CNPs and dark-quenched peptide-based probes (Figure 6).[59] We expected that CNP could carry a large number of peptide probes and efficiently deliver them to the tumor site, where the MMP-responsive cleavage of the peptide would trigger the release of Cy5.5 and generate NIRF signal. The in vivo utility of this system was investigated in the flank tumor- and colon cancer-bearing mouse model, and significant NIRF signal recovery in the tumor tissue was observed. Furthermore, the peptide-based probe without CNP displayed weaker signal in the tumor tissue, and this finding indicates that this nanoparticle system is advantageous for in vivo targeted delivery. Further applications of this system on other diseases or drug delivery have been accomplished or are ongoing in our laboratory.[60]

5. Concluding Remarks

In this Account, we have described our rational strategies about theranostic nanoparticles for in vivo targeted delivery of imaging agents or drugs. On the basis of physicochemical optimization, receptor-mediated cell targeting, and stimulus-responsive release at the target site, we developed novel nanoparticles and applied them successfully to both in vivo diagnosis and therapy.[23] These studies also highlight the importance of in vivo molecular imaging techniques to develop nanoparticles for targeted delivery. In accordance with the old proverb, "Seeing is believing," observing in vivo distribution and target site accumulation of nanoparticles could provide valuable insight for further optimization of them.[4] For this purpose, we have mainly used fluorescence and radio imaging, and these types of in vivo imaging studies could save a large amount of time and effort for achieving goals.

In addition, some researchers often overlook the importance of biocompatible materials for further application in real clinical fields. For clinical applications, the biocompatibility and excretion of nanoparticles are essential, and approval for their biomedical usage by the Food and Drug Administration (FDA) should be sought.[61] Therefore, we have obtained our chitosan derivative and hyaluronic acid from biological sources, used PEG approved by the FDA, and used biodegradable PAE for nanoparticle fabrication.

Various nanoparticles are currently being developed for in vivo imaging and therapy, and this Account could provide valuable information for the design, development, and optimization of such nanoparticles. We hope that novel theranostic nanoparticles will realize ideal personalized medicines in the near future and contribute greatly to optimized therapy for individual patients in clinical fields.[62]

BIOGRAPHICAL INFORMATION

Heebeom Koo was born in 1980 in Anyang, South Korea. He received his B.S. in 2002 and his Ph.D. in 2009 from the Department of Chemistry at Seoul National University under the guidance of Dr. Jong-sang Park. His Ph.D. thesis involved the design and development of novel biodegradable polymeric carriers for drug and gene delivery. He is currently conducting postdoctoral research at the Center for Theragnosis in KIST under the supervision of Dr. Ick Chan Kwon. His research interests include molecular imaging, drug delivery, and gene delivery for diagnosis and therapy.

Myung Sook Huh was born in 1969 in Seoul, South Korea. She received her Ph.D. from the Department of Microbiology and Immunology at the Seoul National University, College of Medicine, Korea, under the supervision of Dr. Ik-Sang Kim. Her previous work includes the development of novel antibacterial vaccines and drug delivery systems. She joined Dr. Kwon's group at the Center for Theragnosis in KIST in 2008 as a postdoctoral researcher. Currently, her research interests include the development of molecular imaging nanoprobes and novel gene therapeutics for cancer therapy.

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Soon Hong Yuk was born in 1959 in Seoul, South Korea. He is currently a professor in College of Pharmacy at Korea University. He received his Ph.D. from the Department of Chemistry, Korea Advanced Institute of Science and Technology (KAIST) in 1987. Then, he joined in the Department of Pharmaceutics and Pharmaceutical Chemistry at the University of Utah as a postdoctral fellow from 1987 to 1989. Also, he worked in Korea Research Institute of

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Kuiwon Choi was born in 1958 in Busan, South Korea. He is currently the Head of the Biomedical Research Institute in KIST. He received his B.S. and M.S. degrees from the College of Engineering at Seoul National University, and his Ph. D. in Bioengineering from University of Michigan in 1991. After postdoctoral training at Henry Ford Hospital in Detroit, he joined KIST in 1993. He served as an Editor-in-chief of the *Journal of Biomedical Engineering Research* (1998−2003), a president of the Korean Society of Biomechanics (2006−2007), and also an International Advisory Committee Member of Asian Pacific Association of Biomechanics. His main research interest is medical device systems and is now expanding to the development of new diagnostic and therapeutic systems utilizing molecular imaging techniques.

Kwangmeyung Kim was born in 1970 in Busan, South Korea. He is a principle research scientist at the Center for Theragnosis in KIST. He received his Ph.D. in 2003 from the Department of Materials Science and Engineering at Gwangju Institute of Science and Technology (GIST), Korea, under the supervision of Dr. Youngro Byun. He joined Dr. Kwon's group at KIST and developed cancer-specific optical imaging systems. His research focuses on noninvasive cancer-specific molecular imaging and therapeutic/diagnostic nanoprobes; he develops smart nanoplatform technology for future diagnosis and therapy of various diseases. He has published over 80 peer-reviewed papers and has over 20 patents.

Ick Chan Kwon was born in 1959 in Daegu, South Korea. He is currently the Head of the Center for Theragnosis in KIST. He received his Ph.D. in 1993 in pharmaceutics and pharmaceutical chemistry from the University of Utah in 1993. He serves as the president of the Korean Society of Molecular Imaging, as an Associate Editor of the *Journal of Controlled Release*, as an Asian Editor of the *Journal of Biomedical Nanotechnology*, and as a member of several editorial boards. His current research interests are targeted drug delivery with polymeric nanoparticles and the development of smart nanoplatforms for theranosis. He has published over 180 peer-reviewed papers and has given over 60 national and international invited lectures.

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FOOTNOTES

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