The Annual Final Scientific Report:

Development of Convergence Nanoparticles for Multi-Modal Bio-Medical Imaging

Key researchers: Jinwoo Cheon
Affiliation: Department of Chemistry, Yonsei University
Address: 134 Shinchon-dong, Seodaemun-gu, Seoul 120-749, Korea
Tel: 82-2-2123-5631, fax: 82-2-364-7050, email: jcheon@yonsei.ac.kr

Table of Content

1. Abstract
2. Introduction
3. Approach
4. Results and discussions
5. Pay-off
6. Summary
7. References
8. Research outputs
9. Financial reports

* Appendix: The first page and the page including acknowledgement part of the published papers.
### Abstract
The purpose of this project is to develop a novel, highly versatile, multi-functional convergence nanoparticle system for their advanced biomedical applications. Inorganic nanoparticles are now emerging as a promising candidate to revolutionize current science and technology. By utilizing inorganic nanoparticles, it is possible to have the ability to control physical/chemical properties of materials as we desire, which is no allowed incumbent technology. Furthermore, these inorganic nanoparticles exhibit improved physical/chemical properties, compared to classical bulk materials. Such enhanced properties of inorganic nanoparticles make them useful as key components for futuristic nanodevice applications although there have been remarkable progresses in the synthesis of inorganic nanoparticles during the past decade, currently developed nanoparticles possess only simple and basic functions and therefore have difficulties to be utilized in advanced applications. To develop multi-functional convergence nanoparticles, we planed three-year research project. As the first stage, in this year, we fabricated prototype convergence nanoparticles and we first studied multi-functionality of magnetic nanoparticle, MR (magnetic resonance) contrast effect and heat generation ability. Based on the magnetic nanoparticle, we synthesized prototyped convergence nanoparticles by conjugating with optical component and radioisotope. Then, we have accomplished feasibility test on the biological system such as Amyloid β aggregation and lymph node detection.

### Subject Terms
- Bio-applications
- Nanotechnology
1. Abstract

The purpose of this project is to develop a novel, highly versatile, multi-functional convergence nanoparticle system for their advanced biomedical applications. Inorganic nanoparticles are now emerging as a promising candidate to revolutionize current science and technology. By utilizing inorganic nanoparticles, it is possible to have the ability to control physical/chemical properties of materials as we desire, which is not allowed in current technology. Furthermore, these inorganic nanoparticles exhibit improved physical/chemical properties, compared to classical bulk materials. Such enhanced properties of inorganic nanoparticles make them useful as key components for futuristic nanodevice applications although there have been remarkable progresses in the synthesis of inorganic nanoparticles during the past decade, currently developed nanoparticles possess only simple and basic functions and therefore have difficulties to be utilized in advanced applications. To develop multi-functional convergence nanoparticles, we planned three-year research project. As the first stage, in this year, we fabricated prototype convergence nanoparticles and we first studied multi-functionality of magnetic nanoparticle, MR (magnetic resonance) contrast effect and heat generation ability. Based on the magnetic nanoparticle, we synthesized prototyped convergence nanoparticles by conjugating with optical component and radioisotope. Then, we have accomplished feasibility test on the biological system such as Amyloid β aggregation and lymph node detection.
2. Introduction

Inorganic nanoparticles with unique quantum mechanical properties have the potential to revolutionize current classical mechanics-based science and industry. By utilizing inorganic nanoparticles, it is possible to have the ability to control physical/chemical properties of materials as we desire, which is not allowed in current technology. Furthermore, these inorganic nanoparticles exhibit improved optical, magnetic, and electronic properties, compared to classical bulk materials. When these tiny materials get into biological system, their exceptionally enhanced properties arising from such nanoscale properties can enable them to be utilized as key probes and vectors for next-generation ultra-sensitive detection and highly efficient therapeutic systems. During past few years, researches on this field have been explosively carried out and some of successful studies have shown such possibilities in part. However, despite such remarkable progresses in bio-medical applications of inorganic nanoparticles, currently developed nanoparticles possess only simple and basic functions and therefore have difficulties to be utilized in advanced applications. For the successes in the next-generation nanotechnology-based bio-medical applications, it is necessary prerequisite to secure advanced inorganic nanoparticle systems. For that reason, we proposed a novel, highly versatile, multi-functional convergence nanoparticle system for their advanced biomedical applications (Scheme 1). We fabricated prototype convergence nanoparticles by integrating individual nanoparticle components with its unique function into a single nanosystem.

Scheme 1. Convergence nanoparticle systems.
3. Approach

1) Approach

A. Fabrication of magnetic nanoparticles for simultaneous diagnosis and hyperthermia treatments

Magnetic nanoparticles have novel magnetic properties arising from nanoscale phenomena which allow versatile application in biological fields. For example, magnetic nanoparticles have been widely used as a diagnostic agent for MRI. Besides their usage as a MRI contrast agent, magnetic nanoparticle can be also used as a heat generator for hyperthermia. Under alternating current (AC) magnetic field, the electron spins of magnetic nanoparticle are flipped along with the external magnetic field change. During this process, the energy difference between spin states generates heat which can deteriorate diseased tissues.

In order to fabricate high quality magnetic nanoparticle, we have been developed high temperature molecular precursor method. Among the various magnetic nanoparticles, we focused on fabrication of MnFe$_2$O$_4$ which has superior magnetic property compared to other types of metal ferrites.

![Figure 1. Magnetic nanoparticle for disease diagnosis and therapy.](image)

B. Fabrication of a convergence nanoparticle system

Convergence nanoparticles can be fabricated through 1) self-assembly of nanoparticles using molecular assemblers or 2) selective secondary nucleation on top of the seed nanoparticles. Since the chemical/biological molecules can be designed and synthesized to have high symmetry and have the ability of self-recognition and assembly, the use of these molecular assemblers enables the systematic construction of multi-component convergence nanoparticles. In the case of the formation of convergence nanoparticles through secondary nucleation on the seed, modulation of similarity of the lattice geometry between seeds and secondary materials, affinity between two materials such as alloying, electro chemical potential differences, activity of a specific surface and catalytic activity is important.
C. Multi-modal utilizations of convergence nanoparticles

The multi-component convergence nanoparticle system can enable multimodal multiplexing imaging and detection of biological processes by conjugating with bio-active materials. Conventional detection systems are operated independently and each detection system has own advantages and disadvantages. However, convergence nanoparticles can overcome the many shortcomings that are present for single imaging modality methods. As a model case study, we are planning to utilize magnetic-optical convergence nanoparticles for the dual-mode detection of proteins (amyloid β protein) or lymph node.

2) **Uniqueness of approach**

Although there have been remarkable progresses on the bio-medical applications of nanoparticles, currently developed techniques have been limited to mono-functional single component system and the realization of multi-modal biomedical applications of nanoparticles has been elusive. Convergence nanoparticle possesses i) multi-functionalities which enables accurate multi-modal diagnosis and pin-pointing therapy and have potential for ii) collective physical/chemical properties arising from synergistic communications between nanoparticle components and highly enhanced properties. With developed convergence nanoparticle system, it is possible to perform not only multi-mode detection system but also further applications such as sensing, information, navigation, and actuation in a single nanosystem. Therefore it can revolutionize current biomedical sciences and techniques including biosensor, cell trafficking, and cancer diagnosis.

3) **Research contents**

The 1st stage (2007.03-2008.02): Ability study of proto-type dual-mode convergence nanoparticles for their dual mode detection

- Fabrication of magnetic nanoparticles as a MRI contrast agent and heat generator
- Fabrication of proto-type convergence nanoparticle via combination of magnetic nanoparticle and fluorescent dye
- MRI and optical detection of amyloid β (Aβ) protein by utilizing the developed convergence nanoparticles

The 2nd /3rd stage (2008-2009): Convergence nanoparticles for multi-modal biomedical applications
4. Results and discussion

4-1. Fabrication of magnetic nanoparticles for simultaneous diagnosis and hyperthermia treatments

At the early stage of this project, we have investigated on the heat generation efficiency of magnetic nanoparticles, which make possible them to use for both cancer diagnosis and therapy. Among the various nanoparticles, MnFe₂O₄ (MnMEIO; manganese doped magnetism engineered iron oxide), which previously showed excellent MR contrasting effect (Nature Medicine 2007), was investigated.

MnFe₂O₄ are synthesized via high temperature decomposition of MnCl₂ and Fe(acac)₃ (acac = 2,4-pentadione) in the presence of oleylamine and oleic acid as capping molecules following known methods. Synthesized nanoparticles are 15 nm and high monodispersity. (Figure 2a)

Synthesized nanoparticles (1 mg/ml (Mn+Fe)) are mixed with cancer cell (MCF7) and heat generation efficacy was measured with the cell viability under the AC magnetic fields (500kHz). Live cells are stained with Calcein-acetoxymethyl(AM) Assay and shown as green color. As shown in figure 2, MnMEIO nanoparticle shows significant cancer cell killing effect with the AC magnetic field irradiation compared to the case without AC magnetic field.

![Figure 2. (a) TEM image of synthesized MnMEIO nanoparticles. When synthesized nanoparticles are mixed with cancer cells, compared to cancer cells without AC magnetic field (b), cancer cells which are applied AC magnetic Field shows significant](image)

4-2 Fabrication of convergence nanoparticles and their utilization on the detection of the biological events.

4-2-1 Magnetic nanoparticle for Aβ aggregation detection

In next stage, we fabricate prototype convergence nanoparticles, Co@Pt-Au, through epitaxial growth on the seed.

First, Co@Pt was synthesized following the previously reported method. Then, Au is then deposited on the Co@Pt nanoparticles via hydrogenation of AuCl(PPh₃) by purging with a 4% H₂/Ar mixture. The Co@Pt-Au nanoparticles obtained in this
manner have a heterodimer structure composed of 6 nm Co@Pt and 9 nm Au. Synthesized nanoparticles show both superparamagnetic properties from Co@Pt and optical properties from gold component. (Figure 3)

Figure 3. (a) Schematics and (b) TEM images of synthesized Co@Pt-Au. The synthesized nanoparticles show superparamagnetic properties (c) and have red color from Au component (d).

As a feasibility test, we examined Aβ assembly detection. For that purpose, nanoparticles conjugated with neutravidins (NTV) which can successfully recognize biotin functionalized Aβ assemblies. Because Aβ peptide forms various assemblies from oligomer to protofibril and to fibril as their concentration increases, assembled nanoparticles due to Aβ aggregates are expected to show increased signal compared to free nanoparticles. In the T2 image of Co@Pt-Au solution with various concentration of Aβ₄₀ peptides (0, 0.5, 1, 5, 10, 32, 80, 250 μM), these samples showed that significant contrast changes take place from none to dark signal. The color coded images of T2 weighted signals more clearly depict the changes taking place as the Aβ₄₀ concentration increases. Especially, at the Aβ concentration below 10 μM, the sharp changes on ΔT2 value is observed compared to solutions with Aβ₄₀ concentration upper than 10 μM at which fibril forms. It demonstrates that MRI is a highly sensitive probe for detecting the early stages of Aβ₄₀ self-assembly (protofibril).

Figure 4. MR signal changes depending on degree of Aβ assemblies. MR image
shows gradual changes from none to grey and to black and color coded image shows the signal changes more clearly.

4-2-1 PET-MRI dual-modal nanoprobe for lymph nodes detection

By hybridization of magnetic nanoparticle, MnMEIO with radioisotope \(^{124}\text{I}\), we could successfully perform the dual modal nanoprobe for PET and MRI imaging. Because PET radionuclide \(^{124}\text{I}\) can be directly conjugated to tyrosine in serum albumin (SA), SA coated MnMEIO is an efficient platform for formation of PET/MRI hybrid nanoprobes. (Figure 5a) Figure 5 depicts in vivo PET, MR, and PET/MR fusion images of SLN of Sprague-Dawley rats after \(^{124}\text{I}-\text{SA-MnMEIO}\) nanoprobes (320 \(\mu\text{g (Fe)/kg}\), \(^{124}\text{I}\) activity: 100 \(\mu\text{Ci}\)) were injected to the right forepaw (injection site: I). In the coronal view of PET (Figure 5b), brachial lymph node, which is the first SLN, is clearly visualized as red hot spots after administration of \(^{124}\text{I}-\text{SA-MnMEIO}\) probes. Similarly, black spot is also observed by MR imaging (white arrow, Figure 5c) and the position of brachial lymph nodes is perfectly matched in PET/MR fusion image (figure 5d)

![Figure 5. (a) Dual modal PET-MRI probe and schematics of lymph node imaging. (b) MRI, (c) PET, (d) PET-MRI fusion image of dual probe injected mouse. (I: injection site)](image-url)
5. Pay-off

This year project is for the demonstration of prototype convergence nanoparticles so these successful results can make possible to develop advanced convergence nanosystems for ongoing projects (2008~2009). As we described in previous section, convergence nanoparticle can be utilized for the multi-modal imaging because of their integrated properties, which can enhance the diagnostic accuracy and detection sensitivity. In addition, our convergence nanoparticle system also can be potentially further applied to have abilities such as sensing, information, navigation, and actuation in a single nanosystem and therefore can revolutionize current biomedical sciences and techniques including biosensor, cell trafficking, and cancer diagnosis. For example, convergence nanoparticle made by combination of magnetic nanoparticle mentioned in previous session, which has MR contrasting effect and heat generating ability, and fluorescent dye can be utilized as a simultaneous ultra sensitive diagnostic probe and disease treatment agent.
6. Summary

As a first stage in three year project for the development of convergence nanoparticles for multi-modal biological imaging, we successfully demonstrate the basic concepts for the formation of convergence nanoparticles and also find out their capability for the biological imaging. In this project, firstly, (1) we focused on the study of multi-functionality including MR contrasting ability and therapeutic ability of MnMEIO nanoparticles. (2) Then, based on the magnetic nanoparticles, we fabricate prototype convergence nanoparticles, Co@Pt-Au nanoparticles (epitaxial growth) and MnMEIO-radioisotope (hybridization using molecular linker). (3) With developed nanoparticles, we also perform the feasibility test for the detection of the biological event, Aβ assemble and lymph node.

Based on these results, we will further investigate for the development of advanced convergence nanoparticles for the fault free diagnosis of disease.
7. References

8. Research outputs

8-1. Publications

1. Cheon, J. et al.
   “Nanoparticle assisted magnetic resonance imaging of the early-reversible stage of amyloid β self-assembly”
   *Chem. Commun.* **2008**, 2197. [I.F. = 5.141]

2. Cheon, J. et al.
   “A hybrid nanoparticle probe for dual-modality positron emission tomography and magnetic resonance imaging”

8-2. Conferences

1. Cheon, J.
   "Nanomaterials for Biomedical Diagnosis: Convergence Nano-structures and MEIO"

2. Cheon, J.
   "Magnetic Nanoparticles for Bio-Medical Applications"

3. Cheon, J.
   "Fabrication of Hetero-Structured Co@Pt-Au Nanoparticles for the Biological Applications"
   Materials Research Society Meeting, MRS, Boston, MA, U S A, Nov. 27, 2007
9. Financial Reports

<table>
<thead>
<tr>
<th>I. Planned Expenditure</th>
<th>II. EXPENDITURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Nov. 1, 2004~ Oct. 31, 2005)</td>
<td></td>
</tr>
</tbody>
</table>

**SALARIES**

A. SENIOR PERSONNEL: $24,000
   - Jinwoo Cheon: $2,000 * 12 months = $24,000
B. OTHER PERSONNEL: $12,000
   - Jae-Hyun Lee: $1,000 * 6 = $6,000
   - Jin-sil Choi: $1,000 * 6 = $6,000

**D. EQUIPMENT** $0

**E. TRAVEL** $3,000

MRS, Boston
   - Jin-sil Choi:
     - Airfare: $1,800 + Travel Cost: $1,200 = $3,000

**F. TUITION REF 2.12.13** $0

**G. OTHER DIRECT COSTS** $56,200
1. SUPPLIES/MATERIALS $13,250
   * See the detailed materials sheet.
2. COMM’S/SHIPPING $1,000
3. OTHER $3,000
   - telecommunication $50 * 12 = $600
   - office supplies $1,400
   - copies $1,000

**J. TOTAL DIRECT EXPENSES AND FACILITIES AND ADMINISTRATION EXPENSES**
   - Overhead $18,750

Total: $75,000
### Detailed materials sheet

<table>
<thead>
<tr>
<th>Item</th>
<th>Unit price ($)</th>
<th>Amount</th>
<th>Total ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron pentacarbonyl (Strem 26-2800, 250 g)</td>
<td>30.00</td>
<td>15</td>
<td>150.00</td>
</tr>
<tr>
<td>Dicobalt octacarbonyl (Fluka 60811, 25g )</td>
<td>200.00</td>
<td>10</td>
<td>2000.00</td>
</tr>
<tr>
<td>Platinum acetylacetonate (Aldrich 282782, 5g)</td>
<td>500.00</td>
<td>5</td>
<td>2500.00</td>
</tr>
<tr>
<td>Potassium tetrachloroaurate (Riedel 12526, 5g)</td>
<td>500.00</td>
<td>5</td>
<td>2500.00</td>
</tr>
<tr>
<td>Oleylamine (Aldrich O7805, 500g)</td>
<td>130.00</td>
<td>10</td>
<td>1300.00</td>
</tr>
<tr>
<td>Oleic acid (Sigma O1383, 25 g)</td>
<td>150.00</td>
<td>10</td>
<td>1500.00</td>
</tr>
<tr>
<td>Sephadex G-25(Sigma S5772, 25g)</td>
<td>180.00</td>
<td>5</td>
<td>900.00</td>
</tr>
<tr>
<td>TBE buffer (Sigma T4415, 10x, 20 L)</td>
<td>230.00</td>
<td>2</td>
<td>460.00</td>
</tr>
<tr>
<td>M2C2H</td>
<td>165.00</td>
<td>10</td>
<td>1650.00</td>
</tr>
<tr>
<td>1,2-Hexadecanediol, Tech (Aldrich 213748, 50g)</td>
<td>132.0</td>
<td>1</td>
<td>132.00</td>
</tr>
<tr>
<td>Iron(III) acetylacetonate (Aldrich 517003, 50g)</td>
<td>158.00</td>
<td>3</td>
<td>158.00</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td><strong>$ 13,250</strong></td>
</tr>
</tbody>
</table>

*Note: The table above lists the items and their corresponding unit prices, amounts, and totals.*
Nanoparticle assisted magnetic resonance imaging of the early reversible stages of amyloid β self-assembly†

Jin-sil Choi,* Hyuck Jae Choi,† Dae Chul Jang,* Joo-Hyuk Lee† and Jinswoo Cheon†

Received (in Cambridge, UK) 26th February 2008, Accepted 19th March 2008
First published as an Advance Article on the web 11th April 2008
DOI: 10.1039/b802844d

Co@Pt-Au nanoparticles, which have enhanced magnetism and high stability in aqueous media, are utilized in conjunction with MRI to monitor the structural evolution of Aβ assemblies, especially Aβ protofibrils in the early reversible stages.

Self-assembly is a term used to describe the spontaneous and intermolecular force-driven organization of components into ordered structures. Processes of this type play crucial roles in cellular functions, and in the construction of higher-level structures, such as lipid bilayers in cell membranes, double helical DNA and proteins in quaternary structures. In particular, self-assembly of the amyloid β (Aβ) peptides, leading to malfunction of the neural system, is a known pathogenic process in Alzheimer's disease. Recently, Au nanoparticles have been successfully employed for the highly sensitive detection of Aβ assemblies in optical sensing or bio-bar code systems.

In a magnetic resonance imaging (MRI)-based sensing system, advantage is taken of the fact that the assembly of magnetic nanoparticles in aqueous solution leads to a change in the proton nuclear spin–spin relaxation time (T2) of water molecules. Consequently, when used as probes for dynamic biological phenomena, Aβ2 values serve as indicators of not only the switching of magnetic nanoparticles between dispersed and aggregated states, but also the degree of assembly of target molecules. In order to maximize MRI signal enhancing effects, nanoparticles with strong magnetism are desirable. Although ferromagnetic metals, such as Fe, Co, and Ni, possess stronger magnetic moments than that of currently widely used iron oxide nanoparticles, they cannot be directly used for biological applications due to their high reactivity in aqueous environments. In this study, we have developed highly stable metal-based heterodimer nanoparticles, which have both large magnetic moments and high colloidal stability. We have used them as probes for direct MRI observation of Aβ assemblies at early stages of the progressive assembly.

The heterodimer nanoparticles, consisting of a Co magnetic core and a Pt shell that is directly linked to an Au nanoparticle (Fig. 1(a)), are prepared from Co@Pt nanoparticles.† Au is then deposited on the Co@Pt nanoparticles via hydrogenation of AuCl(PPh₃)₃ by purging with a 4% H₂/Ar mixture. The Co@Pt-Au nanoparticles obtained in this manner have a heterodimer structure of roughly 15 nm, composed of 6 nm Co@Pt and 0.6 nm Au (Fig. 1(b)). The measured face-centered cubic (111) lattice sizes of the Pt shell and Au deposition are 2.2 and 2.4 Å, respectively, which are consistent with known values. From energy dispersive X-ray spectroscopy (EDS) analysis, elemental changes corresponding to the Pt shell, Co core, and Au clearly confirm the formation of Co@Pt-Au nanoparticles (Fig. 1(d)). Co@Pt and Co@Pt-Au nanoparticles possess almost identical

![Diagram](image-url)
changes taking place at the early stages of assemblies including protofibrils. On the other hand, at Aβ40 concentrations over 10 μM, the MRI response to the Aβ40 process is not as large. Early stage protofibrils, with strong β2 changes, are in a reversible state. For example, protofibrils that are present at Aβ40 concentrations around 5 μM reversibly disassemble. Only dispersed CoxPr-Au (hydrodynamic size of ~20 nm) is obtained when the protofibril is diluted to 0.1 μM (Aβ40) and kept for 4 d (RST). In contrast, fibrils generated at 100 μM Aβ40 maintain their micro-sized irregular aggregate form without a significant change in their sizes when diluted. Since it is possible to reverse and retard the Aβ protofibril process, the ability to detect Aβ assemblies in their reversible stages is important in the context of Alzheimer’s disease treatment.

In summary, we have demonstrated that CoxPr-Au nanoparticles that have enhanced magnetic properties and high colloidal stability can be used in conjunction with MRI to monitor key structural stages of Aβ assemblies. The exceptional, dramatic changes that take place in MR signals during Aβ assembly enable the detection of Aβ protofibrils in the early reversible stages. This is an important finding because information of this type could be used in a therapeutic approach to Alzheimer’s disease that involves the reversible disassembly of Aβ protofibrils. Furthermore, the magnetic nanoparticle-assisted MRI detection system could be applied as a sensitive probe of protein self-assembly including prions, osynuclein and β-amyloid.

We thank Y.-w. Jun for his helpful discussions and M.-Y. Kim for her graphics work. This work is supported in part by NRI (Rh4-2004-0-1025), NCC (RT-2004-0304-0-016), NCR (RL-2004-024-000-0-0), NanoBio Science & Technology Program (M1050000-219-05M0000-2-8180), the KRC of Fundamental Science & Technology (21C2606-07-259), the BK 21 Project and Seoul Science Fellowship.

Notes and references


This journal is © The Royal Society of Chemistry 2008

Chem. Comm., 2008, 2107-2109 | 2108

Fig. 3 CoxPr-Au-NTV nanoparticles aggregate induced by Aβ40 (a) TEM and magnified TEM images (cont.) show progressive structural changes of nanoparticle assemblies, depending on Aβ40 concentration (0, 0.5, 5 and 10 μM). (b) DLS data show the size change of CoxPr-Au-NTV-Aβ40 assemblies in the Aβ40 concentration increase.
A Hybrid Nanoparticle Probe for Dual-Modality Positron Emission Tomography and Magnetic Resonance Imaging

Jin-sil Choi, Jeong Chan Park, Hyunsoo Nah, Seuntae Woo, Jeun Oh, Kyeong Min Kim, Gi Jeong Cheon, Yongmin Chang, Jongwoo Yoo* and Jinwoo Cheon*

As the accurate imaging of biological targets becomes an increasingly important tool for understanding basic biological phenomena and for fault-free diagnosis of various diseases, current single-modality imaging methods tend to be inadequate. Therefore, multimodal imaging can be an essential tool in state-of-the-art imaging research and also standard practice in the clinic. By combining dual- and triple-modality methods, many shortcomings that are present for single-modality imaging methods can be overcome. For example, the simultaneous use of positron emission tomography (PET), for its highly sensitive functional imaging, and computed tomography (CT), for its ability to provide clear anatomical information, has been demonstrated for the early detection of cancer. Several combinations of imaging methods with different modalities, such as magnetic resonance (MR), optical and PET/multimodal optical fluorescence (NIRF), are possible. Recently, the development of a dual-modality diagnostic instrument for PET/MRI imaging (MRI) has been demonstrated.

In addition to the instrumental advances of the diagnostic hardware, the development of nanoparticle-based probes is a prerequisite for successful multimodal diagnostics. Quantum dots have been labeled with radioactive or paramagnetic metal ions to serve as MRI-based dual-modality probes. Superparamagnetic iron oxide (SPIO) nanoparticles have been labeled with fluorescent dyes for MR/optical dual-modality imaging. The SPIO nanoparticle conjugated with 60Cu and fluorescent dye as a new class of trinodal probe was demonstrated for magnetic detection in atherosclerotic plaques by using PET/CT imaging in comparison to MRI.

Herein, we report a magnetic-nanoparticle-based PET/MRI probe and the evaluation of its effectiveness as an in vivo dual-modality imaging agent. Nanosilicate imaging and three-dimensional tomography are important advantages of PET and MRI. In Figure 1, the imaging characteristics of PET and MRI are compared by using a Darzen phantom filled with a solution of contrast agents. In the PET image, all circles ranging from 1.2 to 4.6 mm in diameter are well resolved (Figure 1A) and it is possible to go further down to a resolution of 250 μm (see the Supporting Information, Figure S1). On the other hand, the PET image shows relatively poor spatial resolution and only circles larger than 5.4 mm in diameter are resolved (Figure 1B). Although the MR probe provides better spatial resolution, in terms of sensitivity the PET probe shows an enhanced contrast effect, with picogram-scale sensitivity compared to the nanogram-scale sensitivity of the MR probe (see below).

Supporting information for this article is available on the website under http://dx.doi.org/10.1002/anie.200801369.

Dr. J. C. Park, Dr. J. Oh, Prof. J. Yoo
Department of Molecular Medicine and Nuclear Medicine
CMRI, Kyungpook National University, Daegu 700-432 (Korea)
Fax: (+82) 52-436-5644
E-mail: yooj@knu.ac.kr
J.-S. Choi, H. Nah, Prof. J. Cheon
Department of Chemistry, Yonsei University
Seoul 130-749 (Korea)
Fax: (+82) 2-364-7650
E-mail: jcheon@yonsei.ac.kr
J. Woo
Department of Biomedical Engineering
Kyungpook National University, Daegu 700-722 (Korea)
Fax: (+82) 52-224-5015
E-mail: jwooj@knu.ac.kr
F. Y. Chang
Department of Molecular Medicine and Diagnostic Radiology
Kyungpook National University, Daegu 700-722 (Korea)
Dr. M. Lim, Dr. G. J. Cheon
Molecular Imaging Research Center
Institute of Radiological and Medical Sciences
Seoul 159-705 (Korea)

This work was partly supported by the NRF (No. 2011-0000169), the Korea Research Council of Fundamental Science & Technology, the National Cancer Institute for Cancer Nanotechnology Excellence, and the World premier program of chemistry and medical college. Production of PEG was supported partly by the KIMR project of MOST and KOSSIF.

17