Development of molecular imaging and nanomedicine in China

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The rapid progress of molecular imaging (MI) and the application of nanotechnology in medicine have the potential to advance the foundations of diagnosis, treatment, and prevention of diseases. Although MI and biomedical nanotechnology are still in a formative phase in China, much has been achieved over the last decade. This article provides a commentary on the development and current status of nanomedicine in China, with a selective focus on Chinese nanoparticle synthesis technology, the development of imaging equipment, and the preclinical application of novel MI probes.

INTRODUCTION

Beginning with the invention of X-ray, medical imaging techniques have evolved through three stages: originally structural imaging, more recently functional imaging, and today molecular imaging. Molecular imaging (MI) is a medical technique that quantitatively and qualitatively interrogates biological processes in living organisms at the cellular and molecular levels.1 MI utilizes specific molecules (i.e., molecular probes or contrasts) to identify subtle biochemical features of cells that characterize physiological or pathological processes. High-sensitivity and low-resolution nuclear medicine techniques have spawned a cadre of small molecule probes, dating back to the era of immunoscintigraphy2; however, the advent of MI for lower sensitivity modalities, such as magnetic resonance imaging (MRI), computed tomography (CT), and ultrasound (US), has required agents with large payloads of relevant contrast materials usually packaged as nanoparticles.

Nanomedicine is a new field of interdisciplinary research, combining the biochemical understanding of pathologic mechanisms with the rules of physics, chemistry, and genetics to synthesize nanosized structures. The interaction of these disciplines in recent years has resulted in a flood of nanoparticle-based contrast agents, each with the potential for improved disease detection, diagnosis, and treatment.5 New nanosystems are uncovering the physical, chemical, and biological constraints and opportunities for early disease detection, patient stratification, and targeted gene and drug delivery approaches.6 Although nascent as a medical science, the potential of nanomedicine already offers tangible new approaches and great hope for overcoming many intractable disease diagnostic issues in cancer,7,8 cardiovascular disease,9 neurology,10 and rheumatology.11 These targeted multifunctional technologies circulate longer, provide high contrast, and deliver therapeutic payloads, expanding the horizon of biomedical imaging in clinical management.12

THE EMERGENCE OF MI IN CHINA

Shortly after the MI concept was proposed, Prof. Yuqing Liu,13 an academic of the Chinese Engineering Academy (CEA), introduced the concept to Chinese radiologists at the ‘Advancing Front of Medical Imaging Academic Symposium of CEA’ in 2000. Although conference attendance was limited, the seeds of the idea were sown. Two years later, the theme of the 194th Fragrance Hill Science Conference was MI, which marked the first national conference on the topic and the formal start of nanomedicine research in China. In the same year, the first MI research center in China was established at Harbin Medical University by Dr. Baozhong Shen, who had returned
from Dr. Ralph Weissleder’s lab at Massachusetts General Hospital, Harvard Medical School. Shortly thereafter in 2004, the ‘First Molecular Imaging Academy Forum in China’ was held at Harbin Medical School. The program drew an abundance of clinical radiologists and interventional physicians already engaged in MI research. Subsequently, the first and second editions of MI Chinese academic monographs, entitled ‘Molecular Imaging’, were published by People’s Medical Publishing House in July 2007 and September 2010, respectively. In 2008, the First Joint U.S.–China Nanobiology and Nanomedicine conference, cosponsored by the CEA and the National Cancer Institute of the U.S. National Institute of Health, convened in Beijing (Figure 1). Subsequent to these events, a notable upsurge in published Chinese nanomedicine research was observed, increasing from 39 PubMed referenced manuscripts in 2004 to 231, a sixfold increase, in 2010 (Figure 2). In parallel, the number of MI centers in China expanded from 5 to 25, a fivefold increase.

**NANOPARTICLES FOR OPTICAL IMAGING**

**Quantum Dots**

Optical imaging is an advantageous, relatively low-cost technique for *in vitro* and *in vivo* imaging of cells and cellular processes. Among the various fluorescent-labeling methods, quantum dots (QDs) have garnered the greatest interest. QDs are defined as semiconductor structures with physical dimensions smaller than the exciton Bohr radius. Usually, this characteristic is associated with semiconductors below 100 nm. QDs have tunable properties dependent upon their nanometer-sized structures, providing biomedical researchers a spectrum of colors to label essential biochemical cellular features in order to probe heretofore-unanswered questions relating to the diagnosis and treatment of diseases.

The cadmium precursor, Cd(CH₃)₂, used in the early synthesis of QDs is extremely toxic, pyrophoric, expensive, unstable at room temperature, and explosive at elevated temperatures. However, a breakthrough occurred in 2000, when Peng et al. identified CdO instead of Cd(CH₃)₂ as a precursor
for the synthesis of CdTe, CdSe, and CdS QDs.\textsuperscript{15} They proposed a simple model to explain the growth of faceted CdSe nanocrystals based on intraparticle diffusion control on the surface of the nanocrystals.\textsuperscript{16}

Although the desired optical benefits of QDs are clear, the hydrophobic character of the surfaces impairs their direct use in biosystems. Several unstable and laborious methods for hydrophobic/hydrophilic phase transfers and surface modification techniques have been pursued, usually spoiled by significant decreases in quantum yield, i.e., optical signal.\textsuperscript{17} The synthesis of QDs by aqueous routes emerged in China and other countries. Gao et al., from the Institute of Chemistry, Chinese Academy of Sciences, explored a water-in-oil (W/O) reverse microemulsion method\textsuperscript{18–20} to prepare fluorescent core–shell CdTe in particles with controllable particle sizes. Fluorescence quantum yield of CdTe encapsulated in the silica particles reached 47\%. Further development of highly fluorescent CdTe/CdS core–shell nanocrystals in SiO\textsubscript{2} produced fluorescence quantum yields of 85\% in water at room temperature.\textsuperscript{21} In 2010, Zhou et al. of Hunan University and Zhejiang University, developed a facile one-pot strategy for aqueous synthesis of silica-hybridized CdTe QDs (SiO\textsubscript{2}-h-CdTe QDs), which was scalable to batch sizes approaching a kilogram.\textsuperscript{22} The advancement of aqueous synthesis chemistry to produce cost-effective QDs with high quantum yield has propelled the research in this field.\textsuperscript{23} Further stabilization of QDs with varying small molecules\textsuperscript{24} has provided chemical handles to accommodate a wide array of options to functionalize the surface for biomarker applications. Chinese scholars, along with other world scientists, have explored and reported the coupling of QDs to antibody,\textsuperscript{25} albumin,\textsuperscript{26} and cells.\textsuperscript{27}

Many groups have developed highly successful procedures for QD staining of cells and tissue specimens. Recently, researchers at the Beijing Institute of Technology exemplified this using a mouse liver hepatoma BNL 1ME A.7R.1 (MEAR) cells. Biotinylated MEAR-specific ssDNA aptamer TLS9a was coupled to streptavidin-functionalized quantum dot, which specifically differentiated MEAR cells from BNL cells. Moreover, the growth and viability of QD-Apt bound to MEAR cells did not affect cell viability by QD-Apt within 84 hours compared to control cells, suggesting that the probe might be biocompatible for live cell imaging.\textsuperscript{28}

QDs continue to be widely applied to optical imaging applications; however, QDs are commonly synthesized with harsh conditions and toxic precursors, their surfaces are difficult to passivate, and they tend to photoblink (i.e., on-off fluorescence emission). Although these traits limit the utility of QDs for clinical use, they stimulated the development of new fluorescent reporters that are less toxic, smaller, and easier to synthesize and conjugate to biomolecules. Fluorescent gold nanoparticles (GNPs), for example, emerged to address this unmet need.

**Gold Nanoparticles**

GNPs were discovered over 100 years ago. These nanoparticles have distinguishing advantages such as modifiable surface chemistry, good biocompatibility, low acute toxicity, and large X-ray cross sections. Small-sized GNPs range in size from 200 nm down to a few gold atoms (<3 nm), which is comparable to the Fermi wavelength and imparts natural fluorescence. As the quantum yields (QY) of GNPs are several orders of magnitude over that of bulk gold (QY = 10\textsuperscript{-10}), optical applications as probes for both \textit{in vitro} and \textit{in vivo} biomarker recognition have been prevalent. In China and elsewhere, improved syntheses of highly stable GNPs with improved control of particle size and shape have received widespread research attention. Wang et al., from the School of Material Science and Engineering at Harbin Institute of Technology in China,\textsuperscript{29} developed technology to produce GNPs with stable fluorescence and a quantum yield reaching 8.6\%. Chang et al.\textsuperscript{10} extended the utility of fluorescent GNPs through functionalization with biologically relevant molecules: PEG, BSA, avidin, and streptavidin.

GNPs have received significant consideration for use in multiple imaging technologies.\textsuperscript{31} Researchers at Shandong Normal University in Jinan, China, reported the incorporation of GNPs as quencher modules in fluorescent probes for DNA damage caused by intracellular hydroxyl radicals (HO\textsuperscript{*}). Their research showed a unique combination of selectivity and high sensitivity and established the potential value of such probes for investigation of HO\textsuperscript{*}-mediated cellular homeostasis and injury.\textsuperscript{32} On the therapeutic front, a nanoscale interfacial phenomenon mediated by GNPs was reported by Huang et al. in 2010. They showed that coadministration with GNPs allowed percutaneous delivery of protein drugs to overcome the skin barrier. They exploited this finding for a noninvasive vaccine delivery strategy based upon the topical coadministration of antigens with GNPs. Robust immune responses elicited in animal studies to date suggest that the potential for needleless transcutaneous vaccination is very good.\textsuperscript{33}
NANOPARTICLES FOR MRI

Synthesis of Ultra-Small Superparamagnetic Nanoparticles for MRI

Ultra-small superparamagnetic iron oxide (SPIO) nanoparticles have been widely used as T2 MRI agents since the early 1990s based on their high magnetic susceptibility, small diameter (10–20 nm), and narrow particle size distribution. Over the past 20 years, the synthesis and surface functionalization of iron oxide nanoparticles have been intensively explored with numerous approaches including: chemical coprecipitation, thermal decomposition, hydrothermal processes, polyol methods, sol–gel reactions, decomposition of organometallic precursors, reactions in steric environments, etc. Chinese scholars have participated in the quest to synthesize high-quality SPIOs.

Although chemical coprecipitation is a common and convenient technique to obtain iron oxide particles, it is often plagued by broad size distributions, poor crystallinity, and variable magnetic properties. Effective means to increase size uniformity were pursued by Hong et al. through the addition of polyelectrolytes as stabilizing agents to produce peroxidized dextran-coated magnetic nanoparticles. The resulting particles were essentially monodispersed and had an average diameter of 8 nm. Wan et al. prepared tunable iron oxide nanoparticles (4–18 nm) by inclusion and manipulation of graft copolymers, poly(glycerol monoacrylate)-g-poly(PEG methyl ether acrylate).

Thermal decomposition methods based on the pyrolysis of organometallic compounds, metal–surfactant complexes, and metal salts have also been used to achieve high-quality iron oxide nanocrystals with monodispersity, high crystallinity, and size tunability. However, this approach yields particles with poor water solubility, which required further surface chemical modification for high-performance magnetic contrast applications. Sun et al. developed a high-temperature reaction of iron(III) acetylacetonate with 1,2-hexadecanediol in the presence of oleic acid and oleylamine to produce monodisperse Fe3O4 nanoparticles with tunable core sizes from 4 to 20 nm. These particles were further adapted for water solubility by addition of a bipolar surfactant. Gao et al. replaced the nonpolar solvents typically used in the synthesis of iron oxide particles with strongly polar 2-pyrrolidone to obtain hydrophilic iron oxide nanocrystals ranging from 4 to 60 nm.

Hydrothermal synthesis of iron oxide is another chemical approach using a solvent under elevated pressures and temperature (i.e., above or below its critical point) to increase solubility and reaction rates between solids. Two principal routes are employed to create ferrites through hydrothermal conditions: (1) hydrolysis and oxidation or (2) neutralization of mixed metal hydroxides. Y. D. Li and his team, in the Department of Chemistry at Tsinghua University, improved the controllable synthesis of Fe3O4 nanoparticles by advantageously using phase transferring processes at solid/solution (water–ethanol) and liquid (ethanol–linoleic acid)/solid (metal linoleate) interfaces in combination with reduction reactions and in situ particle surface coating.

In a polyol process, a metal precursor compound in liquid polyol is heated to boiling and is reduced to form metal nuclei seeds that grow to form magnetic nanoparticles. Cai and Wan developed methods to directly produce magnetite nanoparticles utilizing a modified polyol process. After studying four polyols, ethylene glycol, diethylene glycol, triethylene glycol, and tetraethylene glycol, they determined that only triethylene glycol produced the desired magnetite particles with uniform shape, high crystallinity, and superparamagnetic properties at room temperature. In vitro experiments showed that these magnetite nanoparticles possessed excellent MRI contrast effect, unusual cancer cellular affinity, and good biocompatibility.

Stability is critical to the widespread use of iron oxide nanoparticles under the intended application conditions. Antiaggregation stability is particularly important for in vivo biomedical applications, where there is the potential for serious blood vessel blockages and possibly pulmonary embolism. Stabilizers, such as inorganic materials, surfactants, or polymeric compounds, have been studied as a means of preventing particle sedimentation and improving biocompatibility. Dong et al. produced a core/shell structured Fe3O4/Au using layer-on-layer technique. The Au shell served to protect the Fe3O4 core and present a modifiable surface for further organic functionalization. Yang et al. employed an emulsion method for the synthesis of silica-coated iron oxide nanoparticles with entrapment of biological macromolecules in the pores. Interestingly, Xu et al. used dopamine to functionalize stable iron oxide magnetic nanoparticles and Lu et al. reported manganese-doped superparamagnetic iron oxide (Mn-SPIO) nanoparticles for enhanced imaging of small liver lesions, assessment of liver cirrhosis, and differential diagnosis of other liver diseases. Shi et al. reported labeled mesenchymal stem cells (MSCs) with SPIO in vitro, and dynamically monitored magnetically labeled MSCs transplanted into established swine models of acute liver injury using a clinical 1.5 T MR scanner. Teng’s group has
also achieved a succession of promising results in MR progenitor and in vivo stem cell tracking studies.49–51

Targeted Ultra-Small Superparamagnetic Iron Oxide Nanoparticles
In 2010, researchers from Harbin Medical University in China developed a transferrin conjugate of ultra-small superparamagnetic iron oxide nanoparticle (Tf-USPIO) as a magnetic resonance (MR) reporter probe.52 Tf-USPIO was used to bind cells transfected with retro-ES-TfR in vitro. In mice, subcutaneously implanted with both retro-ES-TfR and empty retrovirus retro-LNCX cells, intravenous Tf-USPIO conjugate produced a greater decrease in T2 relaxation time in the retro-ES-TfR tumors than the control counterparts. They showed the successful use of a TfR reporter gene and Tf-USPIO MR reporter probe, opening the door to further applications in the expanding field of gene therapy.

Paramagnetic Nanoparticles for MRI
Although iron oxide nanoparticles elicit effective dark contrast with T2-weighted (T2w) imaging, bright contrast T1-weighted (T1w) agents are often preferred against the predominantly dark MR image; however, synthesis can be more challenging because of the high payloads of contrast metal required to overcome partial volume dilution. In the past 2 years, a number of publications by Chinese scientists have addressed this challenge. Luo et al.53 achieved an unusually high sensitivity paramagnetic nanoparticle platform by using polycation polyethylenimine conjugated to gadopentetic acid (Gd–DTPA–PEI) as a multilayer coating over silica nanoparticles. This new T1-imaging probe offers a multiplicity of potential uses for future cellular and MI applications. Yang et al.54 synthesized a stable and biocompatible water-dispersible Fe3O4–SiO2–Gd–DTPA–RGD nanoparticle with r1 relaxivity of 4.2 mm−1s−1 and r2 relaxivity of 17.4 mm−1s−1 at the Gd/Fe molar ratio of 0.3:1. These results illustrate the potential to use this agent for both T1w positive and T2w imaging. Zhou et al.55 reported the development of a multimodal nanoprobe, 18F-labeled Gd3+/Yb3+/Er3+ co-doped with NaYF4 nanophosphors, for sensitive MI with nuclear, MR, and optical imaging from the cellular level up to whole-body scale. Wang et al.56 detailed a thrombus-specific P-selectin-targeted paramagnetic contrast agent with high sensitivity to detect occult microthrombi on the intimal surface of endothelium in the femoral vein of dog, which may allow detection of ruptured atherosclerotic plaque in the future. Huang et al.57 reported a series of sub-10-nm nanospheres, nanoplates, and nanocubes of Mn3O4, which may potentially be used as multifunctional bioprobes for cellular imaging and diagnostic applications.

MICROBUBBLES FOR ULTRASOUND
Ultrasound contrast agents (UCA) are typically gas-filled microbubbles, stabilized by a shell (denatured albumin, phospholipid, or cyanoacrylate). The ideal UCA provides high scattering cross section, is nontoxic, and stable in circulation. Conventional high-capacity, low-cost techniques to prepare microbubbles include sonication and high shear emulsification, but such processes yield markedly heterogeneous particle sizes. More advanced preparation technologies have evolved, in China and elsewhere, to better control microbubble size, composition, stability, and uniformity.62–64 These include: membrane emulsification, inkjet printing, electro-hydrodynamic atomization, and microfluidic methods. At the Research Center of Biomedical Engineering of Xiamen University, China, Pan et al.65 prepared US contrast bubbles by combining a sonication method and Shirasu porous glass membrane emulsification technique to incorporate hydroxycamptothecin (HCPT) into a poly lactic acid (PLA) polymeric shell. The HCPT–PLA microbubbles were intravenously administered for combined diagnostic and therapeutic use, also known as a theranostic application.

Although typical US blood pool contrast agents are micron-sized bubbles (2–4 µm), allowing pulmonary transit, the highly reflective particles in circulation or passively adhered to tissues or cells can confound MI specificity and sensitivity. The first US MI agent reported was based on liquid perfluorocarbon nanoparticles,66 which increased acoustic reflectivity when bound to a target, such as a fibrin clot, but provided no contrast when free in circulation. Since that first report, other novel nanosized contrast agents have come forth,67–69 including a nanoscale microbubble contrast agent. Xing et al.70 fabricated a novel biocompatible nanobubble UCA by ultrasonication of a mixture of Span 60 and polyoxyethylene 40 stearate followed by differential centrifugation to isolate the relevant subpopulation from the parent suspensions. These nanobubbles provided excellent power Doppler enhancement when applied in vivo for renal imaging.70 Another example was reported by Wang et al. from Zhejiang University, who prepared nanobubbles incorporating coumarin-6 as a model drug and showed enhanced drug delivery to cells based on the pharmacokinetics of the compound.71
NANOPARTICLES FOR CT

X-ray CT is one of the most dominant diagnostic tools in hospitals in terms of frequency of use and cost. Current blood pool contrast agents for CT are mainly based on iodinated small molecules, which have a high X-ray absorption coefficient compared with nonmetal atoms along with K-edge energy near the centroid of the photon bandwidth. Iodinated blood pool compounds require rapid image acquisition because of their rapid clearance through the kidney. This has led to the development of several iodine-based nanoparticle agents for extended blood pool and potential MI.72–74 However, iodine presents significant safety issues. Unlike established agents that received ‘grandfathered approvals’, new materials will need to address the known safety issues related to iodine sequestration into the thyroid and the induction of acute tubular necrosis, particularly in patients with underlying chronic renal insufficiency.

The development of alternative nanoparticle-based CT contrast agents with longer circulation times has begun. One example is a polymer-coated bismuth sulfide (Bi2S3), a natural ore with sizes ranging from 50 to 250 nm. This agent had pronounced and persistent X-ray contrast in rodents in comparison with commercial iodinated agents.75 Unfortunately, bismuth sulfide is a highly insoluble crystal with a large particle size that provides excellent intravascular contrast but exceeds the kidney excretion threshold (6–8 nm).76–79 Pan et al. have also capitalized on the utility of bismuth for CT contrast imaging, but utilized small, stable bismuth–organo complexes, such as bismuth neodecanoate, to establish high contrast with a vascular constrained nanoparticle that could be readily eliminated from the body.80 In the same report, Pan et al. demonstrated the potential of this approach for fibrin specific spectral CT imaging, opening up a significant healthcare opportunity to detect ruptured plaque in patients presenting to emergency departments with chest pain of unclear etiology.

Gold is often considered for use as a CT contrast agent and as discussed above, it is readily functionalized with homing ligands. A recent study, demonstrated GNP-based imaging using spectral CT for passive uptake by atherosclerotic plaque macrophages in vivo, but like the bismuth sulfide particles, the size of many gold particle-based agents exceed the renal clearance threshold, due to the amount of metal required to overcome the inherent insensitivity of the modality.

In China, there have been several innovative publications engaging GNPs as X-ray contrast agents.81,82 Wang et al.83 reported a successful aqueous gram-scale method for producing high-quality GNP by controlling the reaction kinetics to form homogeneous Au nuclei with controlled growth. Shi et al.84 demonstrated the acute safety of GNPs and suggested that small GNPs could have potential for greater X-ray attenuation than larger ones, depending on the application. Other GNP contrast agents based upon dendrimer,85,86 PEG,87,88 and low-density lipoproteins89 are also under intense study. Complemented by a variety of bio-molecular efforts to enhance targeting effectiveness, CT contrast research based on GNP appears to be growing in China.90,91

PHOTOACOUSTIC IMAGING WITH CARBON NANOTUBES

Carbon nanotubes (CNTs) have garnered worldwide interest as a nanodevice for biomarker probe development. Single-walled carbon nanotubes (SWNTs) are a member of the carbon particle family92 with unique near-infrared intrinsic fluorescence, inherent Raman spectroscopy, and photoacoustic93,94 signal capability. These inherent imaging attributes are associated with graphene, one-atom-thick planar sheets of sp2-bonded carbon atoms densely packed in a honeycomb crystal lattice crudely imagined as atomic-scale chicken wire.92 While developments in CNT research in China have lagged behind other countries, many labs in China are now invested heavily in this research area. Notably, Xiang et al., from South China Normal University, have reported antibody-functionalized SWNTs for early detection of tumors with photoacoustic MI in vivo.95 Much more is expected from this arena of research.

NANOTECHNOLOGY APPROACHES TO DRUG DELIVERY

Nanotechnology for drug delivery, like MI, has gained traction in China. Hu et al. successfully prepared epirubicin (EPI)-loaded solid lipid nanoparticles (EPI-SLNs) as an inhalable treatment of lung cancer. In vitro research suggested that SLNs remained stable during nebulization with an improved respirable fraction compared to EPI solutions. In vivo, the pharmacokinetics of drug concentrations achieved by inhalation of EPI-SLNs was higher in plasma and lungs than that achieved with EPI solutions. These findings suggested the potential of EPI-SLNs as an inhalable delivery system for treatment of lung cancer.96

A sterically stabilized, mitoxantrone-loaded liposome functionalized to target cells over-expressing
of contrast agents. Great attention has been paid to evolved to complement the ever-increasing number PET, and SPECT and various combinations has MI instrumentation for optical, US, MR, CT, THE DEVELOPMENT OF MI over a similar nontargeted approach.97

the significant therapeutic benefit of the targeted agent receptor-mediated endocytosis. They demonstrated of intracellular delivery of mitoxantrone through developed by He et al. to promote the efficiency luteinizing hormone-releasing hormone receptor was improved over Taxol and Abraxane.99

Fibroblast growth factor receptors are overexpressed on the surface of a variety of tumor cells and in the tumor neovasculation, and are popular targets for tumor- and vascular-targeting therapy. Wang et al. demonstrated improved pharmacokinetics and tissue distribution of a novel truncated basic fibroblast growth factor peptide-mediated cationic liposomal paclitaxel (tbFGF-LPs-PTX) over free paclitaxel and a cationic liposomal paclitaxel in tumor-bearing mice. tbFGF-LPs-PTX significantly increased the accumulation in the tumor and prolonged the retention time.98

Luo et al. developed a well-defined, biocompatible amphiphilic telodendrimer system (PEG-b-dendritic oligo-cholic acid) that self-assembles into multifunctional micelles in aqueous solution for efficient delivery of hydrophobic drugs such as paclitaxel. Optical imaging studies in xenograft models demonstrated preferential uptake of the smaller paclitaxel-loaded micelles (17–60 nm) by the tumor, and the larger micelles (150 nm) by the liver and lung. The toxicity and antitumor efficacy profiles of these paclitaxel-loaded micelles in subcutaneous xenograft models improved over Taxol and Abraxane.99

Simultaneous in vivo imaging and delivery of therapeutic products for cancer treatment, so called theranostic agents, have gained the attention of Chinese scientists. Zou et al. utilized an antibody-targeted, fluorescence-labeled SPIO nanoparticle for dual MRI and fluorescence imaging of cancer cells and pH-dependent intracellular drug release. Anticancer drugs doxorubicin, azi do-doxorubicin, MI-219, and 17-DMAG containing primary amine, azide, secondary amine, and tertiary amine, respectively, were entrapped into the IONP coating. In the colon cancer cell line (LS174T), pH-dependent drug release, intracellular distribution, and cytotoxicity were evaluated using microscopy and MTS assay. The IONPs provided simultaneous cancer cell imaging, targeted anticancer drug delivery, and pH-dependent drug release.100

THE DEVELOPMENT OF MI EQUIPMENT IN CHINA

MI instrumentation for optical, US, MR, CT, PET, and SPECT and various combinations has evolved to complement the ever-increasing number of contrast agents. Great attention has been paid to the versatility, speed, sensitivity, and resolution of images acquired from dynamic biological processes. Although the majority of biomedical scanners in China were introduced from foreign countries, Chinese scientists have also contributed new tools protected by independent intellectual property rights. As an example, in the early half of the last decade very few laboratories worldwide had successfully developed systems for in vivo fluorescence tomography of small animals. In 2003, the Institute of Automation at the Chinese Academy of Sciences and the Molecular Imaging Center of Harbin Medical University began to explore the investigation and novel development of optical MI systems protected by international intellectual property rights, respectively.43,84,101–110

This, in conjunction with Guangzhou Zhongke Kaisheng Medical Technology Co., Ltd, established ‘The Center for Research and Development of Molecular Imaging, Institute of Automation, Chinese Academy of Sciences’ (CTDMI), an entity tasked with the utilization and management of these and ongoing achievements in optical MI. CTDMI constructed a bioluminescence tomography prototype system, which incorporated both Western and Chinese advancements in optics technology. The emergent system included a novel fluorescence signal collecting device, a proprietary image signal pretreatment module, and a computer processing system for digital autofluorescence laminography.

Further instrumentation research for small animal fluorescence, PET, MRI, and CT systems is ongoing at other science centers including Tsinghua University and Tianjin University. Wu et al.111 from Tsinghua University pursued scatter correction methodology utilizing a maximum likelihood expectation maximization (MLEM) algorithm based on Poisson mode to compare the sinograms and reconstruct images corrected by MLEM algorithm. Significant improvements in image contrast and scatter correction were reported. The Department of Engineering Physics of Tsinghua University has reported several advancements over the last decade. One significant example was the development of a location sensitive X-ray detector for a hybrid PET/SPECT/CT system comparable to current commercial instruments but with a 30% reduction in manufacturing cost. On April 24, 2009, this instrument, the Neusoft Truesight PET system, was cleared by the FDA, representing a breakthrough for Chinese medical industry. Neusoft is now the only Chinese company and among the very few worldwide that is capable of research, development, and manufacture of PET systems with the freedom to operate under independent intellectual property rights.
ESTABLISHING A CHINESE ACADEMIC COMMUNITY FOR NANOMEDICINE

At present, the MI and nanomedicine centers in China were founded either by clinical doctors and radiologists from medical schools or by material chemistry scientists from comprehensive universities. Very few labs or groups have interdisciplinary collaborations among clinical physicians, radiologists, molecular biologists, chemists, physicists, pharmacists, bioengineers, computer engineers, and bioinformation experts. The interdisciplinary nature of this field remains to be enhanced, especially among colleges and medical institutes. Recently, the beginning of a professional national nanomedicine community has begun to form spontaneously in China to address the limited communication among academic institutions. This imperative has emerged in order to promote academic exchange and development through the Internet, professional periodicals, and other means of sharing key resources and fostering collaborations. Moreover, the importance of developing and recognizing international intellectual property has been fortified as Chinese scientists strive to integrate their novel concepts and discoveries into the greater international fabric of ideas.

CONCLUSION

As a growing field, nanotechnology will potentially alter the methods used to diagnose and treat disease. China has a population of approximately 1.3 billion people representing nearly 20% of the total world population. Although China is noted for traditional medicines, its medical community also strives to offer western medical care to patients comparable to that offered in any country. China, like other nations, has benefited from the ongoing international advancements in medical imaging and drug delivery. Today, the Chinese academic community not only seeks to participate in the development of new technologies but to establish leadership roles in discoveries and developments addressing unique medical issues presented by Chinese population. The development of personalized nanomedicine is recognized as a particularly attractive pathway to enhance early medical care and achieve better individual outcomes. With the number of academic centers rapidly rising along with the frequency of new publications and patents, China is endeavoring to reach a technical critical mass. Achievement of a self-sustaining and vigorous research community has begun. Eventually, the progression of bench level discoveries in nanomedicine will ultimately translate to the clinic through focused collaborations between the government, academia, and pharmaceutical/medical imaging industries of China.

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