2nd International Symposium on

Molecular Imaging and Nanomedicine

August 16-20, 2013

Chengdu, China

Co-organized by Institute of Chemistry, CAS and
West China Hospital, Sichuan University
Supported by 973 Program

2nd International Symposium on

Molecular Imaging and Nanomedicine

August 16-20, 2013, Chengdu, China

Symposium Chair

Prof. Mingyuan Gao

Institute of Chemistry, the Chinese Academy of Sciences

Organizing Committee

Prof. Zhifang Chai

Prof. Jiacong Shen

Prof. Mingyuan Gao

Prof. Yan Zhang

Prof. Fabao Gao

Symposium Secretaries

Dr. Lihong Jing

Ruirui Qiao

Dong Su

Venue

Liyuanxiang Liyage Hotel, No.1 North Renmin Road, Jinniu District,

Chengdu, Sichuan, China

Scientific Program for Symposium

<table>
<tr><th></th><th>Aug. 17</th><th>Aug. 18</th><th>Aug. 19</th><th>Aug. 20</th></tr>
<tr><td colspan="2">Morning</td><td rowspan="12">973 internal discussion</td><td rowspan="24">Departure</td></tr>
<tr><td></td><td>Chairman:
Yan Zhang</td><td>Chairman:
Ick Chan Kwon</td></tr>
<tr><td>08:30-08:45</td><td>Opening Remarks, Mingyuan Gao</td><td></td></tr>
<tr><td>08:45-09:10</td><td>Ick Chan Kwon</td><td>Lily Yang</td></tr>
<tr><td>09:10-09:35</td><td>Guojun Zhang</td><td>Hongyu Chen</td></tr>
<tr><td>09:35-10:00</td><td>Qiangbin Wang</td><td>Kaichun Wu</td></tr>
<tr><td>10:00-10:25</td><td>Shu Wang</td><td>Man Kwan</td></tr>
<tr><td>10:25-10:45</td><td>Coffee break, symposium photo</td><td>Coffee break</td></tr>
<tr><td></td><td>Chairman:
Alexander Eychmüller</td><td>Chairman:
Xiaohu Gao</td></tr>
<tr><td>10:45-11:10</td><td>Xiaohu Gao</td><td>Hans-Joachim Galla</td></tr>
<tr><td>11:10-11:35</td><td>Jianghong Rao</td><td>Hongwei Duan</td></tr>
<tr><td>11:35-12:00</td><td>Hua Ai</td><td>Dongsheng Liu</td></tr>
<tr><td>12:00-12:15</td><td>Chunyan Liu</td><td>Lihong Jing</td></tr>
<tr><td>12:15-13:00</td><td>Lunch</td><td>Lunch</td></tr>
<tr><td colspan="2">Afternoon</td><td rowspan="12">973 internal discussion</td></tr>
<tr><td></td><td>Chairman:
Andries Meijerink</td><td>Chairman:
Lily Yang</td></tr>
<tr><td>14:00-14:25</td><td>Alexander Eychmüller</td><td>Andries Meijerink</td></tr>
<tr><td>14:25-14:50</td><td>Dayang Wang</td><td>Hong Zhang</td></tr>
<tr><td>14:50-15:15</td><td>Jicun Ren</td><td>Zhen Li</td></tr>
<tr><td>15:15-15:30</td><td>Coffee Break</td><td>Coffee Break</td></tr>
<tr><td></td><td>Chairman:
Guojun Zhang</td><td>Chairman:
Jicun Ren</td></tr>
<tr><td>15:30-15:55</td><td>Yan Li</td><td>Maria Francesca Casula</td></tr>
<tr><td>15:55-16:20</td><td>Fan Wang</td><td>Yanglong Hou</td></tr>
<tr><td></td><td>Chairman:
Hans-Joachim Galla</td><td>Chairman:
Dayang Wang</td></tr>
<tr><td>16:20-16:45</td><td rowspan="3">Flash talk of 2 min for each poster presentation*

Poster discussion</td><td>Ivan Kempson</td></tr>
<tr><td>16:45-17:10</td><td>Hao Lei</td></tr>
<tr><td rowspan="2">17:10-</td><td>Poster prize Award*</td></tr>
<tr><td>Closing Remarks by Mingyuan Gao</td></tr>
<tr><td>18:30</td><td>Welcome banquet</td><td>Farewell banquet</td></tr>
</table>

***Award Committee**: Chairman: Prof. Hans-Joachim Galla; Member: Maria Francesca Casula, Xiaohu Gao, Jicun Ren, Kaichun Wu; Secretary: Ruirui Qiao

Award Presenters: Zhifang Chai, Hans-Joachim Galla, Guojun Zhang, Mingyuan Gao, Dayang Wang

August 16, 2013

14:00-20:00 Registration

August 17, 2013

Morning

Section 1 **Chairman: Prof. Yan Zhang**

08:30-08:45 Opening Remarks
Prof. Mingyuan Gao, Institute of Chemistry, CAS

08:45-09:10 *Sensoring, Monitoring and Control of Protease Activities in Theragnosis*
Prof. Ick Chan Kwon, Korea Institute of Science and Technology

09:10-09:35 *Dynamic visualization of cell cycle in living animals: its application in anti-cancer drug discovery*
Prof. Guojun Zhang, Cancer Hospital of Shantou University Medical College

09:35-10:00 *Ag_2S Quantum Dot: A Bright and Biocompatible Fluorescent Nanoprobe in the Second Near-Infrared Window*
Prof. Qiangbin Wang, Suzhou Institute of Nano-Tech and Nano-Bionics, CAS

10:00-10:25 *Design of Multi-Functional Conjugated Polymers for Sensing and Biomedical Applications*
Prof. Shu Wang, Institute of Chemistry, CAS

10:25-10:45 Coffee break, symposium photo

Section 2 **Chairman: Prof. Alexander Eychmüller**

10:45-11:10 *Molecular Imaging and Profiling of Cancer Cells with Multimodality Nanoparticles*
Prof. Xiaohu Gao, University of Washington

11:10-11:35 *Conjugated polymer nanoparticles for in vivo imaging*
Prof. Jianghong Rao, Stanford University

11:35-12:00 *Magnetic Nanocomposites as MRI Probes: Design and Applications*
Prof. Hua Ai, West China Hospital, Sichuan University

12:00-12:15 *Magnetic/Upconversion Fluorescent $NaGdF_4$:Yb,Er Nanoparticle-based Dual-modal Molecular Probes for Imaging Tiny Tumors in vivo*
Dr. Chunyan Liu, Institute of Chemistry, CAS

12:15 Lunch

Afternoon

Section 1 **Chairman: Prof. Andries Meijerink**

14:00-14:25 *Bio-related research on and with nanoparticles from TU Dresden*

	Prof. Alexander Eychmüller, TU Dresden
14:25-14:50	*Cell as a Factory for Humanized Encapsulation*
	Prof. Dayang Wang, University of South Australia
14:50-15:15	*Imaging Fluctuation Spectroscopy Using Gold (silver) Nanoparticle as Probes*
	Prof. Jicun Ren, Shanghai Jiao Tong University
15:15-15:30	Coffee Break
Section 2	**Chairman: Prof. Guojun Zhang**
15:30-15:55	*Quantum dots-based molecular targeted imaging strategies for individualized cancer treatment*
	Prof. Yan Li, Hospital of Wuhan University
15:55-16:20	*Development of RGD-based radiotracers for tumor imaging and therapy: translating from bench to bedside*
	Prof. Fan Wang, Director of Medical Isotopes Research Center, Peking University
Section 3	**Chairman: Prof. Hans-Joachim Galla**
16:20-17:30	Flash talk of 2 min for poster presentations
17:30-18:30	Poster discussion
18:30	Welcome banquet

August 18, 2013

Morning

Section 1	**Chairman: Prof. Ick Chan Kwon**
08:45-09:10	*Theranostic Nanoparticles for Targeted and Image-guided Cancer Therapy*
	Prof. Lily Yang, Emory University School of Medicine
09:10-09:35	*A General Methodology of Oxide Encapsulation*
	Prof. Hongyu Chen, Nanyang Technological University
09:35-10:00	*Molecular Imaging for Gastric Cancer*
	Prof. Kaichun Wu, Fourth Military Medical University
10:00-10:25	*The Role of Bregs on Live Cancer*
	Prof. Man Kwan, The University of Hong Kong
10:25-10:45	Coffee break
Section 2	**Chairman: Prof. Xiaohu Gao**
10:45-11:10	*Nanoparticles and Biological Barriers: Membrane Interaction, Cellular uptake and Passage*
	Prof. Hans-Joachim Galla, University of Münster
11:10-11:35	*SERS-Encoded Plasmonic Vesicles for Cancer Theranosis*

	Prof. Hongwei Duan, Nanyang Technological University
11:35-12:00	*Smart Hydrogels based on DNA self-assembly*
	Prof. Dongsheng Liu, Tsinghua University
12:00-12:15	*Magnetically Engineered Quantum Dots as potential Fluorescence/Magnetic Resonance Dual-modality Molecular Probes*
	Dr. Lihong Jing, Institute of Chemistry, CAS
12:15-13:00	Lunch
Afternoon	
Section 1	**Chairman: Prof. Lily Yang**
14:00-14:25	*Quantum Dot-Dye Nanoparticles as Probes for Lipid Dynamics*
	Prof. Andries Meijerink, Utrecht University
14:25-14:50	*PET Molecular Imaging in the Evaluation of Stem Cell Therapy*
	Prof. Hong Zhang, the Second Affiliated Hospital of Zhejiang University
14:50-15:15	*Ultrasmall Inorganic Nanoparticles for Bioimaging*
	Dr. Zhen Li, University of Wollongong
15:15-15:30	Coffee Break
Section 2	**Chairman: Prof. Jicun Ren**
15:30-15:55	*Shape-controlled Mangetic Nanoparticles for MRI and Hyperthermia*
	Dr. Maria Francesca Casula, University of Cagliari
15:55-16:20	*Multifunctional Magnetic Nanoparticles for Targeted Cancer Diagnose and Therapy*
	Prof. Yanglong Hou, Peking University
Section 3	**Chairman: Prof. Dayang Wang**
16:20-16:45	*Synchrotron X-ray imaging of nanoparticle fate in biology*
	Prof. Ivan Kempson, University of South Australia
16:45-17:10	*Manganese-based Contrast Agents for Molecular Magnetic Resonance Imaging*
	Prof. Hao Lei, Wuhan Institute of Physics and Mathematics, CAS
17:10-	Poster prize Award
	Closing Remarks by Prof. Mingyuan Gao, Institute of Chemistry, CAS
18:30	Farewell banquet
<u>August 19, 2013</u>	
08:30-12:00	973 internal discussion
12:00-13:00	Lunch
14:00-18:00	973 internal discussion
<u>August 20, 2013</u>	
	Departure

Flashtalk and Poster Presentations*

16:20-18:30, August 17, 2013

Chairman: Prof. Hans-Joachim Galla

Flashtalk

16:20-16:22	Luciferase reporter system for monitoring endogenous microRNAs Prof. Yan Zhang, Nanjing University
16:22-16:24	Application of synchrotron radiation microscopy in the study of the bioeffects of nanomaterials Prof. Qing Huang, Shanghai Institute of Applied Physics
16:24-16:26	Mouse lymphatic endothelial cell targeted probes: anti-LYVE-1 antibody-based magnetic Nanoparticles Prof. Yi Liu, First Hospital of China Medical University
16:26-16:28	Sequentially Light up Cysteine and Homocysteine Based on Kinetic Difference of Probe-Analyte Reactions Prof. Jingzhi Sun, Zhejiang University
16:28-16:30	Preparation and surface modification of tissue-engineered vascular stents Prof. Jiansheng Su, Tongji University
16:30-16:32	In Vivo Near Infrared FRET Imaging of Nanoparticle Accumulation and Dissociation Kinetics Yiming Zhao, Utrecht University
16:32-16:34	Magnetically Engineered Cd-free Quantum Dots as Dual-modality Probe for Fluorescence/Magnetic Resonance Imaging of Tumors Ke Ding, Institute of Chemistry, CAS
16:34-16:36	Facile deposition of continuous gold shell on Tween-20 modified aggregates of Fe_3O_4 nanoparticles Prof. Jiaqi Zhuang, Jilin University
16:36-16:38	Surface engineering of gold nanoparticles for in vitro siRNA delivery Enyu Zhao, Institute of Chemistry, CAS
16:38-16:40	Affibody Modified and Radiolabeled Gold-Iron Oxide Hetero-nanostructures for Tumor PET, Optical and MR Imaging Prof. Huimao Zhang, Stanford University
16:40-16:42	Insight into the Energy Levels of Semiconductor Nanocrystals by a Dopant Approach Prof. Renguo Xie, Jilin University

16:42-16:44 Ultrasmall Magnetic Nanoparticles for T_1 and T_2 Dual Contrast Magnetic Resonance Imaging
Dr. Fengqin Hu, Beijing Normal University

16:44-16:46 Gelification: An Effective Measure for Achieving Differently Sized Biocompatible Fe_3O_4 Nanocrystals through a Single Preparation Recipe
Dr. Qiaojuan Jia, South China Normal University

16:46-16:48 Wash-free magnetic oligonucleotide probes-based NMR sensor for detecting the Hg ion
Prof. Chuanlai Xu, JiangNan University

16:48-16:50 Tunable Near-Infrared Localized Surface Plasmon Resonance of $Cu_{2-x}S$ Nanocrystals via Incorporation of Zinc Ions
Prof. Aiwei Tang, Beijing JiaoTong University

16:50-16:52 Magnetic iron oxide nanoparticles-Tumor detection and BBB transport applications as MRI contrast agent
Ruirui Qiao, Institute of Chemistry, CAS

16:52-16:54 Novel Split-Luciferase-Based Genetically Encoded Biosensors for Noninvasive Visualization of Rho GTPases
Weibing Leng, West China Hospital, Sichuan University

16:54-16:56 Investigations of the Anchoring Group Effects of PEG ligands on the Relaxivity of Fe_3O_4 Nanoparticles for Achieving High Performance MRI Contrast agents
Jianfeng Zeng, Institute of Chemistry, CAS

16:56-16:58 The cumulative analysis of promoter methylation alterations by the cationic conjugated polymer-based FRET
Prof. Libing Liu, Institute of Chemistry, Chinese Academy of Sciences

16:58-17:00 Quantitative evaluation of spontaneous plasticity of corticospinal projections after rat spinal cord injuries by in vivo diffusion tensor imaging
Jichun Liao, West China Hospital, Sichuan University

17:00-17:02 Quantum Dot-Antisense Oligonucleotide Conjugates for Multifunctional Gene Transfection, mRNA Regulation, and Tracking of Biological Processes
Dr. Yilin Li, Peking University School of Oncology, Beijing Cancer Hospital & Institute

17:02-17:04 The role of Snail in early diagnosis of colorectal cancer metastasis
Prof. Jun Du, Sun Yat-sen University

17:04-17:06 One-Step Continuous Synthesis of Ultrasmall Watersoluble Fe_3O_4 Nanocrystals: Influence of Flow Rate on Saturation Magnetization
Mingxia Jiao, Institute of Chemistry, CAS

17:06-17:08	Rational design of "smart" aptamers Prof. Dihua Shangguan, Institute of Chemistry, CAS
17:08-17:10	Activatable Near-Infrared Fluorescent Probe for In Vivo Imaging of Fibroblast Activation Protein-alpha Jinbo Li, Nanjing University
17:10-17:12	$NaGdF_4$ Nanoparticle-Based Molecular Probes for MR Imaging of Intraperitoneal Tumor Xenografts in vivo Prof. Yi Hou, Institute of Chemistry, CAS
17:12-17:14	Multimodality imaging assessments of response to metformin therapy for breast cancer Yi Mao, West China Hospital, Sichuan University
17:14-17:16	Bi-functional Superparticles Assembled by Fluorescent $CuInS_2$-ZnS Quantum Dots and Amphibious Fe_3O_4 Nanocrystals Xiaoyu Sun, Institute of Chemistry, CAS
17:16-17:18	Lectin-conjugated Fe_2O_3@Au core@shell nanoparticles as dual mode contrast agents for in vivo detection of tumor Xiuxia He, Changchun University of Science and Technology
17:18-17:20	Polymer Composite Beads Preparation and Preliminary Application. Zhenyu Gao, Institute of Chemistry, CAS
17:20-17:22	Co-evolution of tumor microenvironment revealed by QDs-based multiplexed imaging Min Fang, Zhongnan Hospital of Wuhan University
17:22-17:24	A study focused on gastric cancer stromal microenvironment based on quantum dots labeled molecular probes Chunwei Peng, Zhongnan Hospital of Wuhan University
17:24-17:26	Computer-based Image Studies on Tumor Nests Mathematical Features of Breast Cancer and Their Clinical Prognostic Value Linwei Wang, Zhongnan Hospital of Wuhan University
17:26-17:28	pH sensitive ratiometricprobe for monitoring the intracellular and extracellular pHs simultaneously Jin Zhou, Institute of Chemistry, CAS
17:28-17:30	PCR mediated nanoscale magnetic assembled sensor for DNA detection Hua Kuang, JiangNan University
17:30-18:30	Poster discussion

***Five excellent posters will be nominated by Poster Award Committee headed by Prof. Hans-Joachim Galla and awarded at the end of the symposium.**

Catalog of Abstracts

Invitation Talks

Posters

Sensoring, Monitoring and Control of Protease Activities in Theragnosis

Ick Chan KWON

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Intrinsic issues that are associated with chemotherapy, particularly in cancer treatment, include early disease detection, efficient drug delivery with adequate drug dose to reach tumor region, and monitoring therapeutic responses. These issues have facilitated the integration of imaging and therapeutic functions in a single platform to further optimize the therapeutic outcomes based on the imaging information. Since theragnosis allow in vivo real-time imaging of the diseased site, monitoring the biodistribution of drug and determining the optimal therapeutic efficacy following treatments, they have been considered as alternatives and ideal solutions to achieve maximal therapeutic efficacy with minimal unwanted side effect, which enable to attain personalized medicine.

Recently, nanoparticles have received a great interest an application for diagnosis and therapy. Since nanoparticles possess intrinsic features that are often required for drug delivery system and diagnosis, they have potential as platforms for integrating imaging and therapeutic functions, simultaneously. Especially, molecular imaging with theragnostic nanoparticles makes it possible not only to provide useful information for monitoring drug delivery, drug release, and therapeutic efficacy of drug, but also to determine whether the patients are likely to respond to a therapy. To achieve these goals, a variety of imaging techniques have been used, including near-infrared fluorescent (NIRF) imaging, magnetic resonance imaging (MRI) and nuclear imaging (SPECT and PET).

Imaging and monitoring of nanoparticles after systemically administered in living systems play key roles in the development of theragnostic nanoparticles to optimize their physicochemical properties. It has become clear that imaging drug delivery can assist in analyzing the drug delivery and in predicting the therapeutic efficacy of cancer-targeted nanoparticles. This presentation will highlight our recent advances that have been made in the development of multifunctional nanoparticles and the applications of these nanoparticles into theragnostic nanomedicine.

Dynamic visualization of cell cycle in living animals: its application in anti-cancer drug discovery

Guojun Zhang, Zhihong Chen, Ruijun Zhao, Caiwen Du, Jing Liu

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Development of anti-cancer drugs that target the certain phase of cell cycle is of high interest because many agents that cause mitotic arrest or block DNA synthetic phase, resulting subsequent cell death. For example, imaging the mitotic arrest would be useful for evaluation of anti-cancer drugs under development in animal models. In the previous published work, we have generated a construct, consisting of the N-terminus of cyclin B1 fused to luciferase and controlled by the cyclin B promoter, serving as an mitotic phase reporter. We demonstrated that this reporter is regulated in a cell cycle-dependent manner and is accumulated in mitotic phase in cellular assays. In subcutaneous tumor models, non-invasive longitudinal measurement of the bioluminescent signal showed an up-regulation of cyclin B consistent with mitotic arrest induced by taxanes, anti-mitotic anti-cancer compounds. Our results demonstrate that the cyclinB-Luc reporter can be used *in vivo* to determine whether a compound can cause M phase arrest, or targets a molecular pathway that affects cyclin B turnover. This work has been published in "Moleclar Imaging and Biology".

In adition, we have applied the technology to non-invasively monitor S phase or G1 phase by genetically engineering Skp2 or cyclin E to luciferase in living subjects. Thus, the advantage of this protocol will enable to generate various reporters to non-invasively monitor biological process *in vivo*.

Ag_2S Quantum Dot: A Bright and Biocompatible Fluorescent Nanoprobe in the Second Near-Infrared Window

Yejun Zhang[1], Yan Zhang[1], Guosong Hong[2], Hongjie Dai[2], Qiangbin Wang[1]

[1]*Suzhou Institute of Nano-Tech and Nano-Bionics, Chinese Academy of Sciences, Suzhou, China.*
[2]*Stanford University, Stanford, United States.*
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Fluorescent imaging in the second near-infrared window (NIR-II, 1.0~1.4 μm) is appealing due to minimal autofluorescence and negligible tissue scattering in this region, affording maximal penetration depth for deep tissue imaging with high feature fidelity. Simulations and modeling studies suggested that fluorophores with emission in the 1000-1320 nm NIR-II region could significantly improve signal-to-noise ratio compared to those emitting at 650-950 nm (NIR-I). Recent efforts have been devoted to identifying NIR-II emitting agents for *in vivo* imaging applications. Quantum dots (QDs) such as PbSe, PbS, and CdHgTe with NIR emission have been successfully developed. However, the highly toxic nature of Pb, Cd and Hg is of concern for *in vivo* applications. Therefore, highly biocompatible NIR-II fluorescent probes that do not contain Cd, Pd or Hg will facilitate biological imaging in this beneficial spectral region. Herein, we first reported a new type of NIR QDs, Ag_2S QDs, with emission in the NIR-II region.

1) Highly selective *in vitro* targeting and imaging of different cell lines were achieved using biocompatible NIR-II Ag_2S QDs with different targeting ligand.
2) *In vivo* imaging of early-stage tumor with Ag_2S QDs was also achieved. Video-rate dynamic contrast-enhanced imaging revealed deep inner organs and tumor in mice.
3) *In vivo* real-time visualization of lymphatic structures, blood flow, and angiogenesis mediated by a subcutaneous xenograft 4T1 mammary tumor utilizing Ag_2S QDs.
4) PEGylated-Ag_2S QDs are mainly accumulated in the reticuloendothelial system (RES) including liver and spleen after intravenous administration and can be gradually cleared, mostly by fecal excretion, without appreciable toxicity to the treated mice over a period of 2 months as evidenced by blood biochemistry, hematological analysis and histological examinations.

Reference:

1. Du, Y.; Xu, B.; Fu, T.; Cai, M.; Li, F.; Zhang, Y.; Wang, Q. *J. Am. Chem. Soc*. **2010**, 132, 1470-1471.
2. Zhang, Y.; Zhang, Y.; Hong, G.; Chen, G.; Li, F.; Dai, H.; Wang, Q. *ACS Nano* **2012**, 6, 3695-3702.
3. Hong, G.; Robinson, J. T.; Zhang, Y.; Diao, S.; Antaris, A. L.; Wang, Q.; Dai, H. *Angew. Chem. Int. Ed*. **2012**, 51, 9818-9821.
4. Li, C.; Zhang, Y.; Wang, M.; Zhang, Y.; Chen, G.; Li, L.; Wu, D.; Wang, Q. *Submitted*.
5. Zhang, Y.; Zhang, Y.; Hong, G.; He, W.; Zhou, K.; Yang, K.; Li, F.; Chen, G.; Liu, Z.; Dai, H.; Wang, Q. *Biomaterials* **2013**, 34, 3639-3646.

Design of Multi-Functional Conjugated Polymers for Sensing and Biomedical Applications

Shu Wang

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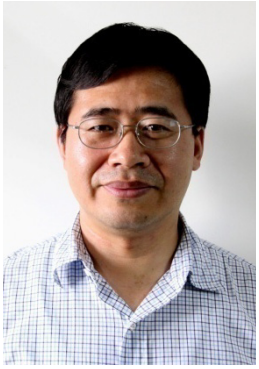

Water-soluble conjugated polymers (CPs) provide a unique platform for chemical and biological sensors in view of their optical signal amplification effect. Our recent studies showed that these polymers could be used for detecting gene modifications, such as single nucleotide polymorphisms (SNPs) and DNA methylation. Genotyping of SNPs will take a deep insight into understanding and clinically diagnosing the complex diseases. The DNA methylation plays a key role in control of gene expression, genomic integrity maintenance and cancer origin. We use CPs/DNA complexes combing with fluorescence resonance energy transfer (FRET) processes to assay SNP genotyping and DNA methylation, thus offering new assay strategies based on conjugated polymers. In recent years, the drugs integrating recognition, imaging and therapeutic functions have attracted more and more attention. They are expected to become a new strategy for the treatment of major diseases. We developed a new technique for preparing multicolor microparticles based on the self-assembly of bacteria and conjugated polymer nanoparticles (CPNs). They can be successfully applied for cell imaging and optical barcoding. A polythiophene porphyrin dyad was prepared for effectively killing neighboring cells. This multifunctional material that simultaneously provides therapeutic action and image the results provide new strategies for the treatment of various diseases. A cationic poly(p-phenylene vinylene) derivate bearing polyethylene glycol (PEG) side chains was also synthesized and used for selective recognition, imaging and killing of bacteria over mammalian cells. This material exerts a far-reaching impact on the future development of antimicrobial materials. These results exhibit that the multi-functional conjugated polymers are ideal platforms for recognition, imaging and disease therapy.

Reference:

1. C. Zhu, L. Liu, Q. Yang, F. Lv, S. Wang, *Chem. Rev.* **2012**, 112, 4687-4735.
2. H. Yuan, H. Chong, B. Wang, C. Zhu, L. Liu, Q. Yang, F. Lv, S. Wang, *J. Am. Chem. Soc.* **2012**, 134, 13184-13187.
3. X. Feng, G. Yang, L. Liu, F. Lv, Q. Yang, S. Wang, D. Zhu, *Adv. Mater.* **2012**, 24, 637-641.
4. Q. Yang, D. Ying, W. Wu, C. Zhu, H. Chong, J. Lu, D. Yu, L. Liu, F. Lv, S. Wang, *Nature Communications* **2012**, 3: 1206.
5. C. Zhu, Q. Yang, F. Lv, L. Liu, S. Wang, *Adv. Mater.* **2013**, 25, 1203-1208.

Molecular Imaging and Profiling of Cancer Cells with Multimodality Nanoparticles

Xiaohu Gao

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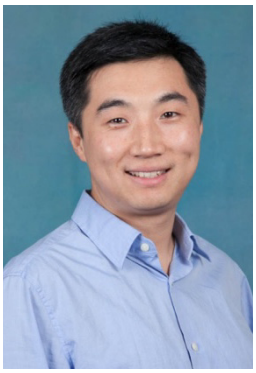

Metal and semiconductor nanoparticles in the 1-10 nm size range are of considerable current interest, not only because of their unique size-dependent properties but also their dimensional similarities with biological macromolecules (e.g., nucleic acids and proteins). These similarities could allow an integration of nanotechnology and biology, leading to major advances in medical diagnostics, prognostics, and targeted therapeutics. In this talk, I present recent development of multimodality nanoparticles for tumor cells detection, isolation, and molecular analysis.

Conjugated polymer nanoparticles for in vivo imaging

Jianghong Rao, Kanyi Pu, Adam Shuhendler, Liqin Xiong

Molecular Imaging Program at Stanford, Department of Radiology, Stanford University, CA 94305, USA
Email: jrao@stanford.edu

This presentation will cover our recent work in developing novel nanoparticle based imaging probes and sensors for in vivo molecular imaging. Conjugated polymer nanoparticles have emerged as a promising class of fluorescent probes due to many attractive properties such as high light harvesting efficiency and lack of toxic metals. The examples covered in the talk will include our development of self-luminescing near infrared (NIR) nanoparticles for lymph node mapping and cancer imaging[1], and near infrared nanoprobes for dual-color fluorescence imaging of reactive oxygen and nitrogen species during inflammation, injuries, and drug-induced liver toxicity[2]. Last, I will introduce a new strategy in designing nanoparticle probes for in vivo imaging and apply it to image tumor apoptotic response to chemotherapy with positron emission tomography (PET) in a mouse model[3].

Reference:

1. Xiong, L, Shuhendler, A. L., Rao, J. *Nature Communications* **2012**, 3, 1193 doi: 10.1038/ncommons2197.
2. Pu, K., Shuhendler, A. L., Rao, J. *Angewandte Chemie in press.*
3. Shen, B., Jeon, J., Palner, M., Ye, D., Shuhendler, A. L., Chin, Rao, J. *Angewandte Chemie in press.*

Magnetic Nanocomposites as MRI Probes: Design and Applications

Hua Ai[1,2]

1. National Engineering Research Center for Biomaterials, Sichuan University, China
2. Department of Radiology, West China Hospital, Sichuan University, China
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Self-assembly of nanoparticles has created many advanced nanostructures with unique properties. Superparamagnetic iron oxide (SPIO) nanoparticles are of special interests because of broad applications in electronic devices, magnetic resonance imaging (MRI), thermal therapy, cell separation, etc. Most high quality SPIO nanocrystals are synthesized in organic phase at high temperatures, and they are not soluble in water. In this presentation, we will discuss how to stabilize SPIO nanoparticles in aqueous phase with the help of functional polymers and how to form controlled structures through self-assembly.

In our approach, polymeric micelles are used as carriers with SPIO nanocrystals located inside the hydrophobic core and protected by the hydrophilic corona in water. Different amphiphilic polymers including polyester-poly(ethylene glycol) (PEG), lipid-PEG, polysaccharide-polyester, and alkylated polyelectrolyte were chosen for loading of nanocrystals. SPIO nanoparticles form unique clustering structures inside micelle cores as verified from transmission electron microscopy. These hybrid nanocomposites are still superparamagnetic at room temperature, and the T2 relaxivity can be tuned by controlling the degree of clustering. In addition, small molecule weight lipid micelles can also encapsulate multiple SPIO nanoparticles and the whole structure is further stabilized through multilayers of polyelectrolytes. These SPIO nanocomposites can generate strong MRI signal contrast both in vitro and in vivo. These hybrid nanocomposites can serve as sensitive MRI probes for early diagnosis, monitoring of therapeutic efficacy and other bioimaging applications. Design of small moleucle paramagnetic probes and conjugation to polymeric carriers will also be discussed.

Reference:

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Magnetic/Upconversion Fluorescent $NaGdF_4$:Yb,Er Nanoparticle-based Dual-modal Molecular Probes for Imaging Tiny Tumors in vivo

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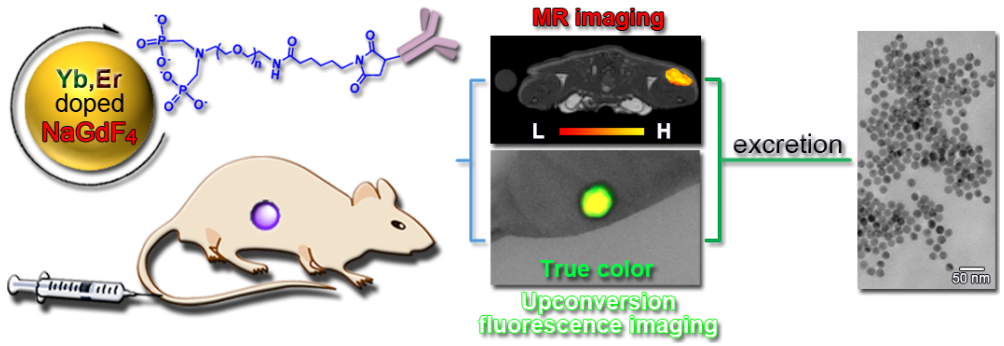
Detection of early malignant tumors remains clinically difficult, developing ultra-sensitive imaging agents is therefore highly demanded. Owing to the unusual magnetic and optical properties associated with f-electrons, rare-earth elements based nanometer-sized particle are very suitable for creating functional materials potentially useful for tumor imaging. Here we report new approaches for size control synthesis of magnetic/upconversion fluorescent $NaGdF_4$:Yb,Er nanocrystals and their applications for imaging tiny tumors *in vivo*. By independently varying F^-:Ln^{3+} and Na^+:Ln^{3+} ratios, the size and shape regulation mechanisms were investigated. By replacing the oleic acid ligand with PEG2000 bearing a maleimide group at one end and two phosphate groups at the other end, PEGylated $NaGdF_4$:Yb,Er nanoparticles with optimized size and upconversion fluorescence were obtained. Accordingly, a dual modality molecular tumor probe was prepared, as a proof of concept, by covalently attaching anti-tumor antibody to PEGylated $NaGdF_4$:Yb,Er nanoparticles through "click" reaction. Systematic investigations on tumor detections, through magnetic resonance imaging and upconversion fluorescence imaging, were carried out to image intraperitoneal tumors and subcutaneous tumors *in vivo*. Owing to the excellent properties of the molecular probes, tumors smaller than 2 mm was successfully imaged *in vivo*. In addition, pharmacokinetic studies on differently sized particles were performed to disclose the particle size dependent biodistributions and elimination pathways.



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Bio-related research on and with nanoparticles from TU Dresden

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Currently, we conduct synthetical efforts to prepare radiolabelled emitting semiconductor nanoparticles (NPs). Tracking of emissive NPs in biological and medical environments has been demonstrated by a number of groups on various routes. We, e.g., infiltrated lipid droplets with core-shell-NPs and with this were able to contribute qualitatively to answers to open questions in the context of lipid metabolisms[1]. The simultaneous labeling with radioactive material aims at a deeper understanding of the underlying bio-processes on a quantitative level. We will line out our thoughts regarding appropriate synthesis schemes with respect to minimizing the intake and handling of radioactive material as well as first results[2].

Since a few years, hydro- and aerogels based on semiconductor, metal and metaloxide NPs are accessible. Their superior properties are largely related to their light weight, open pore structure and large accessible inner surfaces[3]. The youngest member of this class of materials is a mixed ZnO/Pd aerogel which shows very good performance in the methanol steam reforming[4].

This is mentioned only to set the scene for another bio-related project we currently follow in which we study the co-assembly of semiconductor NPs and enzymes into functional architectures in the field of sensing. We fabricated enzyme encapsulated mercaptosuccinic acid capped CdTe hydrogels using the sol-gel method. The porous three dimensional NP hydrogel turned out to be an adequate encapsulation medium for enzymes acting both a bio-catalysis and a fluorescence signaling unit, and was taken as a multi-functional platform in the development of optical biosensors[5]. Both enzyme-encapsulating hydrogels and xerogels exhibited a good sensing ability to the example analyte. As a versatile enzyme entrapment matrix, the NP gels offer great potential in the development of various enzyme-based biosensors and portable sensing devices.

Acknowledgements

The author is indepted to the DFG for funding under DFG EY 10-1, 16-1 and 16-2, to the Alexander von Humboldt foundation for fellowships granted to Dr. Wei Liu, Dr. Yipei Juan, Dr. Dan Wen and Dr. Chengzhao Zhu, and to the CAS for the grant of a Visiting Professorship.

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Cell as a factory for humanized encapsulation

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Enormous efforts are being put in developing colloidal based drug delivery systems, which encapsulate cytotoxic drugs in a vehicle and release them in a controlled manner. However, synthetic carriers, developed thus far, are hampered by rapidly clearance in the body, for example by phagocytes, possibly due to the non-natural surface characteristics in terms of chemistry, morphology, and mechanics. To circumvent this important challenge, we have developed an innovative encapsulation methodology – using living cells as factories to produce cell membrane capsules (CMCs) that can encapsulate a variety of drugs and nanoparticles (NPs).[1] The functions of the membranes and cytoplasms of parental cells are well preserved in CMCs, and can be harnessed to provide an unprecedented mechanism for controlled loading and release of active substances, e.g., by using functional pumps such as multidrug resistance protein (MRP) channels. CMCs are non-cytotoxic and can effectively minimize recognition and internalization by macrophages, thus evading immune attack in the body. Hence the CMCs provide the first intrinsically biocompatible and functional drug delivery and release vehicles. Importantly, CMCs can be harnessed from a wide range of natural or recombinant cells, enabling them to be manufactured with tailored membrane and cytoplasm functionalities. On the other hand, CMCs are almost identical to cells without nuclei, but they are abiotic and intrinsically robust, allowing easy study of a number of biological processes occurring at the cellular level. Furthermore, they will also raise exciting new opportunities to modulate the global immune system and address generic immunological problems.

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Imaging Fluctuation Spectroscopy Using Gold (silver) Nanoparticle as Probes

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In the paper, we present a novel single particle method, named as imaging fluctuation spectroscopy (IFS) based on a quasi total internal reflection (qTIR) imaging configuration and strong resonance light scattering of silver nanoparticles. The principle of IFS is similar to fluorescence correlation spectroscopy (FCS) and it is based on measuring the resonance light scattering fluctuations in a small volume due to Brownian motion of single nanoparticles. We firstly established a highly sensitive IFS system. In this new system, a millimeter-scale hole is employed to efficiently separate nanoparticle scattering light from the background reflected beam and an electron multiplying charge-coupled device (EMCCD) is used as an array detector. The IFS system was successfully used for detection and imaging of single silver nanoparticles in solution. Furthermore, we developed the model of IFS according to the theory of FCS method, and systematically investigated the effects of certain factors such as particle concentration, viscosity of the solution, hardware binning and software binning and accumulation time on IFS measurements using silver nanoparticle as a model sample. Our results showed that experimental data were in good agreement with IFS theoretical model. This new method is multiplexing, spatially resolved and free of photobleaching, which may be well suitable for study on heterogeneous systems, such as, the motion of proteins on cell membrane in the future.

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Quantum dots-based molecular targeted imaging strategies for individualized cancer treatment

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Cancer is one of the most serious health threats worldwide. It has long been recognized that cancer is not merely a local problem, but a complex systemic disease. Many processes regulating tissue and organ development are hijacked by cancer. Among these, invasion and metastasis are the most fundamental properties of cancer biology and the root cause of cancer death. It has been well documented that cancer microenvironment plays an important role in cancer progression via the co-evolution of cancer cells and stroma. One urgent task is to develop novel approaches to let us "see" the rich hidden information in cancer microenvironment simultaneously so as to further elucidate the complex mechanism of cancer invasion and metastasis. Biochemically functionalized quantum dots (QDs) are a heterogeneous class of engineered fluorescent nanoparticles with unique photo and electronic properties, which make them promising platforms for molecular imaging in clinical cancer research. We applied QDs-based molecular imaging of major cancer biological events such as proliferation, invasion and metastasis, to provide real-time, in situ information for individualized cancer treatment decision-making and cancer invasion mechanisms studying.

The QDs-based real-time and in situ cancer detection produced highly sensitive and specific molecular images of liver, breast and gastric cancers. In liver cancer animal models, the QDs-based images could vividly show subcutaneous tumor mass growth, recurrence and lung metastasis. Moreover, this technique can help continuously monitor cancer progression in living animal models. Particularly important information obtained from such analysis is that the tumor mass margin is much more active than centre, which signifies the necessity for wider resection margin during surgical resection of tumor, in order to reduce cancer recurrence. In breast cancer research, QDs-based imaging and quantitative analysis could reveal five distinctive subtypes. Combining the information of ER, PR and HER2 expression levels, it could be found that at least 15% of the breast cancer patients are over-treated, while another 20% of patients are under-treated in current clinical practice. Thus the new QDs-based molecular classification could help select individualized therapy for more appropriate treatments. In QDs-based molecular imaging of cancer microenvironment researches, we developed a theory of co-evolution of cancer cells and their microenvironment. Studies of type IV collagen in liver cancer indicated that there indeed is a complex and constant spatial co-evolution between liver cancer cells and stroma. And the continuous process of type IV collagen degradation and re-patterning makes stroma harder but more fragile and less resistant to cancer invasion. Further multiplexed

imaging of liver cancer microenvironment indicated tumor heterogeneity is universal as the manifestation is not only in cancer nests but also in tumor stroma. Based on simultaneously imaging key elements in the cancer microenvironment such as macrophages, type IV collagen, cancer angiogenesis, and tissue destructive metalloproteinases each plays important roles in cancer invasion, 5 characteristics and 4 patterns of cancer invasion were revealed. These patterns are closely related to tissue destruction and the survival of the patients. And also we have found that "invasion units" consisted of cancer cells, macrophages and cancer angiogenesis were crucial during cancer progression and the more "invasion units" indicated the poorer prognosis.

Therefore, based on such information, we concluded a pulse mode of cancer invasion. In terms of clinical implication, the potential significance of this "pulse-mode" theory is as following: (1) Strategies to decrease ECM stress, delay or block tumor nests "burst" could be helpful to curb cancer invasion and migration; (2) For cancer treatment, modulating tumor microenvironment should be highlighted, in addition to reducing growth and proliferate activity of cancer cells.

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Development of RGD-based radiotracers for tumor imaging and therapy: translating from bench to bedside

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The cell adhesion molecule integrin $\alpha_v\beta_3$ is an important player in the process of angiogenesis. In the last decades, a series of radiolabeled Arg-Gly-Asp (RGD) peptides targeting integrin $\alpha_v\beta_3$ have been prepared and optimized for positron emission tomography (PET) and single-photon-emission computed tomography (SPECT) imaging of integrin $\alpha_v\beta_3$ expression. Several promising radiotracers have been tested in clinical trials. In this talk, our latest preclinical and clinical results on developing new RGD radiotracers for tumor-targeted imaging, radionuclide therapy, and treatment monitoring will be presented.

Theranostic Nanoparticles for Targeted and Image-guided Cancer Therapy

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Highly heterogeneous cancer cells represent the major challenge in the treatment of human cancer. Novel diagnostic and therapeutic agents that enable personalized cancer therapy hold great promise for effective treatment of drug resistant human tumors while minimizing systemic toxicity. We have developed a targeted and image-guided cancer therapy approach that takes advantages of multifunctionality of nanoparticles with abilities of tumor targeting, high capacity of drug loading, and multimodality imaging in combination with advanced molecular imaging methods (1-5). Receptor targeted magnetic iron oxide nanoparticles (IONPs) developed by our group are targeted to epidermal growth factor receptor, Her-2/Neu, IGF-1R, and urokinase plasminogen activator receptor (uPAR), which are biomarkers highly expressed in many types of human cancers. These receptor-targeted IONPs have capacity to carry single or multiple therapeutic agents for drug delivery, near infrared fluorescence, spectroscopic optical imaging, photoacoustic, and magnetic resonance imaging (MRI). They are also designed to overcome physical and intrinsic barriers that reduce efficiency of drug delivery and confer drug resistance in human cancers. We have shown specificity and sensitivity of optical and MR imaging using the nanoparticles as targeted molecular contrast agents in orthotopic human breast, pancreatic, and ovarian cancer xenograft models (1-3). The development of biomarker targeted MRI nanoparticle probes should allow determining the level of biomarker expression in tumors using a non-invasive imaging approach for selection of the appropriate patients for targeted therapy. Based on the targeted imaging nanoparticles, we further developed methods to encapsulate or conjugate chemotherapy drugs into the nanoparticles. Efficacy of targeted therapy and MRI-monitoring drug delivery and response after systemic delivery of the theranostic nanoparticles has been demonstrated in orthotopic human breast, pancreatic and ovarian cancer xenograft models in nude mice (4-5). Since drug resistant residual tumors contain nanoparticles that produce optical signals, we applied hand-held optical imaging devices for detection and removal of drug resistant tumor lesions in the surgical cavity to prevent local recurrence and distant metastasis. The ultimate goal of our research is to translate this biomarker targeted therapy and image-guided treatment and surgery protocol into clinical applications for personalized management of cancer patients.

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A General Methodology of Oxide Encapsulation

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Growing oxide shells on seed nanoparticles requires the control of several processes: (a) the nucleation and growth of the shell material; (b) the "wetting" of the shell material on the seeds; and (c) the aggregation of the nanoparticles. These pro-cesses are influenced by a number of factors, many of which are related. Without understanding the inter-dependence of these contributing factors, it is difficult to circumvent problems and achieve rational synthesis. We first did a case study on encapsulating Au nanoparticles with ZnO to understand the multiple roles of polyvinylpyrrolidone (PVP) and their dependence on other factors. Then, we developed a general method for coating ZnO on a variety of seeds, including metals, oxides, polymer nanoparticles, graphene oxide and carbon nanotube. This method can be further extended to include Fe_3O_4, MnO, Co_2O_3, TiO_2, Eu_2O_3, Tb_2O_3, Gd_2O_3, β-$Ni(OH)_2$, ZnS, and CdS as the shell materials. The understanding obtained in this systematic study will aid rational design and synthesis of other core-shell nanostructures.

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Molecular imaging for gastric cancer

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Molecular imaging is considered to be a reliable and objective method for cancer research and drug evaluation. It greatly shortens the research span and save research expenses. To facilitate gastric cancer research, we established orthotopic gastric cancer model and established GI cancer imaging platform, e.g. self-built BLT-FMT system and corresponding algorithm for image registration and infusion.

Novel imaging probes is indispensable for molecular imaging and associated with imaging quality. Therefore, we developed versatile probes and evaluate their imaging potential in cancer diagnosis. We discovered novel tumor vasculature targeting peptide by phage-displayed libraries, GX1 and GEBP11. By conjugating with isotope and fluorescent dye, we successfully tracked the stomach tumor and realized tumor specific diagnosis through multi-imaging methods, including SPECT, PET, Cerenkov as well as fluorescence imaging. In addition, based on above peptides, we developed two novel anti-cancer agents, GX1-rmhTNFα and ^{131}I-PEG-$(GEBP11)_3$, and evaluated the biodistribution, pharmacokinetics as well as therapeutic efficacy with the help of molecular imaging means.

MGb2 is a monoclonal antibody which is associated with gastric cancer progression and prognosis. In order to assess the tumor proliferation and prognosis using two imaging modalities with one probe, we developed dual modality probe MGb2-Cy5.5-Fe_3O_4. MRI and fluorescence imaging showed consistent observation results. Importantly, we also discussed different conjugate methods for MGb2, and assessed its effects on imaging and labeling efficiency.

Endoscopic molecular imaging is a novel trend with promising future, especially for GI tumors because of its unique anatomical structure compared with other solid tumors. MG7-Ag, which is a specific molecular marker of gastric cancer, was labelled with fluorescent agents to enable *in vivo* real-time imaging by confocal laser endomicroscope (CLE). Targeted molecular imaging of tumors and non-neoplastic tissue were successfully achieved in gastric-cancer cell lines, xenograft models, and surgical or biopsy specimens of patients with gastric cancer. Moreover, specific fluorescent signals were observed in gastric cancerous tissue in patients during *in vivo* real-time endomicroscopic imaging after topical application of fluorescently labelled MG7 antibody. The fluorescent molecular signal detected on fresh human specimens correlated well with immunohistochemical findings, and the interobserver agreement of semi-quantitative grading of confocal images was also excellent.

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The role of regulatory B cells on liver cancer

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Regulatory B cells (Bregs) play important roles in autoimmune diseases, but their function in hepatocellular carcinoma (HCC) progression remains unclear. This study for the first time investigated the distribution of intrahepatic B cells and circulating Bregs population at the level of phenotypes as well as functionality in HCC patients. The mechanisms of Bregs regulating liver tumor cells were further explored in a series of in vitro and in vivo functional studies. Firstly, the percentage of B cells at tumor margin region was significantly higher than that in tumor or non-tumor region. Increased intrahepatic B cells at tumor margin were positively associated with HCC progression, tumor invasive features such as venous infiltration and encapsulation, and more tumor recurrence. In addition, HCC patients had a significant higher percentage of circulating Bregs than healthy people. Increased circulating Bregs were positively correlated with HCC stages, tumor multiplicity and venous infiltration. Secondly, our in vivo study firstly revealed that human Bregs promoted HCC tumor growth independent of Tregs in SCID mice. The migration of Bregs into tumor in mice was further confirmed by in vivo imaging and histology. Finally, the molecular mechanism of Bregs promoted proliferation and migration of HCC cells was proved by direct cell-cell interaction via CD40/CD154 signaling in vitro. Coculture of Bregs and HCC cells also induced CD40/CD154-dependent cytokines secretion. In conclusion: Human Bregs promoted HCC growth and invasiveness by directly interacting with HCC tumor cells through CD40/CD154 signaling pathway. Bregs might be both a prognostic marker and a therapeutic target for HCC.

Active and mediated Transport across the Blood-Brain Barrier in vitro

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The central nervous system (CNS) is protected by the blood– brain barrier (BBB), which is mainly composed of capillary endothelial cells connected by narrow tight junctions, which prevent paracellular diffusion of polar molecules. In addition to its protective function, the BBB ensures sufficient nutrient supply of the brain by regulating the transport of endogenous compounds and controlling their selective and specific uptake, efflux and metabolism. A special transport feature is the so-called multi-drug resistance (MDR). ATP depended efflux pumps (ABC-transporters) prevent the treatment of brain diseases by active export of drugs from the brain back into the blood stream.

This paper will introduce an in vitro porcine brain derived cell culture system that closely resembles the BBB in vivo. The cells express the tight junctions thus forming a firm barrier, which could be easily quantified by impedance spectroscopy measuring the electrical resistance. Mainly due to the presence of the MDR more than 95% of potentially active compounds are not able to overcome the BBB in a pharmacologically sufficient concentration.

To facilitate brain availability various delivery and targeting strategies to overcome the BBB are currently under investigation[1]. One focus of our work is the expression and the regulation of the activity of different ABC transporters in the brain with special interest on the ABCC3 transporter, which has been reconstituted in proteoliposomes and which was shown to act in a cooperative manner with respect to transport and ATPase activity[2]. Inhibition of the ABC transporters will enhance brain availability of drugs.Another possible approach to overcome the barrier may be the use of surface modified and biologically degradable polymeric nanoparticles as drug carriers. Another approach proposed by us is the induction of a reversible disruption of the barrier by nanoparticles, which offers the possibility to use these particles as specific opener of the BBB. Instead of incorporating the therapeutic agents into the NP, the drugs may cross the BBB after being applied simultaneously in a Trojan Horse mechanism[3].

In another approach we use of chemically modified enzymes or nanoparticles to cross the BBB. With this concept we increased the brain uptake of therapeutically enzymes to cure enzyme defects in neuronal cells[4]. Another example is the transfer of iron oxide nanoparticles as contrast agents in MRI diagnosis. We have shown that these nanoparticles functionalized by lactoferrin are transferred to the brain by receptor-mediated transcytosis with an excellent in vivo/in vitro correlation[5].

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SERS-Encoded Plasmonic Vesicles for Cancer Theranosis

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This talk will cover our recent progress in developing bioconjugated plasmonic vesicles assembled from SERS-encoded amphiphilic gold nanoparticles for cancer-targeted drug delivery. This new type of plasmonic assemblies with a hollow cavity can play multifunctional roles as delivery carriers for anticancer drugs and SERS-active plasmonic imaging probes to specifically label targeted cancer cells and monitor intracellular drug delivery. We have shown that the pH-responsive disassembly of the plasmonic vesicle, stimulated by the hydrophobic-to-hydrophilic transition of the hydrophobic brushes in acidic intracellular compartments, allows for triggered intracellular drug release. Because self-assembled plasmonic vesicles exhibit significantly different plasmonic properties and greatly enhanced SERS intensity in comparison with single gold nanoparticles due to strong interparticle plasmonic coupling, disassembly of the vesicles in endocytic compartments leads to dramatic changes in scattering properties and SERS signals, which can serve as independent feedback mechanisms to signal cargo release from the vesicles. The unique structural and optical properties of the plasmonic vesicle have made it a promising platform for targeted combination therapy and theranostic applications by taking advantage of recent advances in gold nanostructure based in-vivo bioimaging and photothermal therapy and their loading capacity for both hydrophilic (nucleic acids and proteins) and hydrophobic (small molecules) therapeutic agents.

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Smart Hydrogels based on DNA self-assembly

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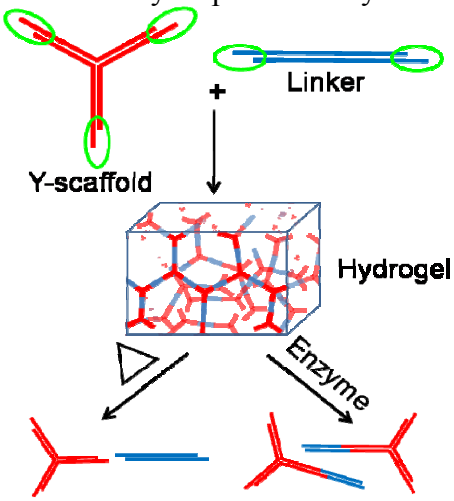
The reversible responsiveness of DNA secondary structures to environmental stimuli has enable to facilitate responsive devices and materials based on pure DNA or hybrid systems. Based on sequence and structure design, we have prepared a pH responsive hydrogels entirely made of DNAs. This hydrogel is formed by cross-linking a single type DNA Y-unit building block through the formation of inter-unit i-motif structures. The fast transformation of i-motif has enabled such DNA gel to respond quickly to environmental pH changes to controllably trap and release cargos (i.e. GNPs here) in a pH-dependent manner. With additional sequence design, the DNA hydrogels can also reversibly respond to enzymes.



The schematic representation of the DNA hydrogel formation.

In principle, other materials, such as nanoparticles, therapeutic proteins, polymers and even protein producing system could be incorporated into such DNA gel system, allowing the development of functional, responsive biomaterials that have applications in a wide range of disciplines: biosensing, tissue engineering, nano-mechanical devices, and drug delivery etc.

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Magnetically Engineered Quantum Dots as potential Fluorescence/Magnetic Resonance Dual-modality Molecular Probes

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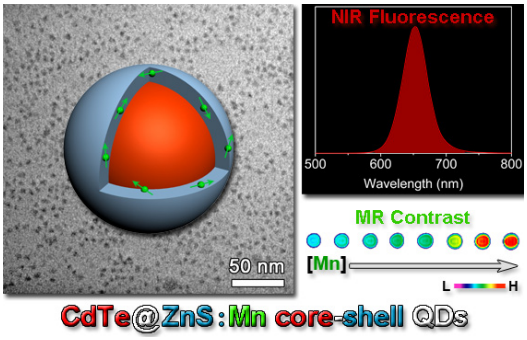

Colloidal semiconductor quantum dots (QDs) doped with transition metal ions have attracted considerable interest as dual fluorescent/paramagnetic probes.[1-6] Manganese doped Core/shell CdTe-based quantum dots (QDs) were synthesized via an aqueous phase approach by surface epitaxial growth of wide-bandgap ZnS shell where the paramagnetic manganese ions reside. Surface chemical engineering by simultaneous epitaxial-type ZnS shell and dopant growth was developed so as to produce core/shell QDs with properly balanced intrinsic photoluminescence emission and paramagnetic merits. The resultant aqueous manganese doped QDs exhibit optimal photoluminescence quantum yield (PL QY) reaching 45% while bearing manganese doping levels in the range of 4.7–9.7%. Systematic investigations by steady-state and time-resolved electronic spectroscopy in combination with structure and composition analysis disclosed the impart of surface manipulations such as both undoped and doped ZnS shell with varying doping levels on the optical properties of resultant core/shell QDs. Further studies based on a combination of electron paramagnetic resonance spectroscopy (EPR) and magnetic resonance (MR) paramagnetic performance exhibiting enhanced longitudinal relaxivity in the range of 5.4–10.7 mM^{-1} s^{-1}, together with the above optical observations, indicate Mn dopant dominantly distributed inside the surface ZnS shell lattice. The current investigations may thus pave a reliable way for developing aqueous phase-based approach for greatly desirable fluorescent/magnetic dual-functional semiconductor nano-platforms.

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Quantum Dot-Dye Nanoparticles as Probes for Lipid Dynamics

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Nanomedicine is a rapidly evolving field which utilizes the properties and physical characteristics of nanomaterials to treat diseases and diagnose at the molecular level[1, 2]. Lipid coated nanocrystal assemblies are among the most extensively investigated nanoparticle platforms for biomedical imaging and therapeutic purposes. However, very few efforts have been addressed to the lipid coating exchange dynamics in such systems, which is key to our understanding of the nanoparticles' coating stability and their interactions with the environment[3].

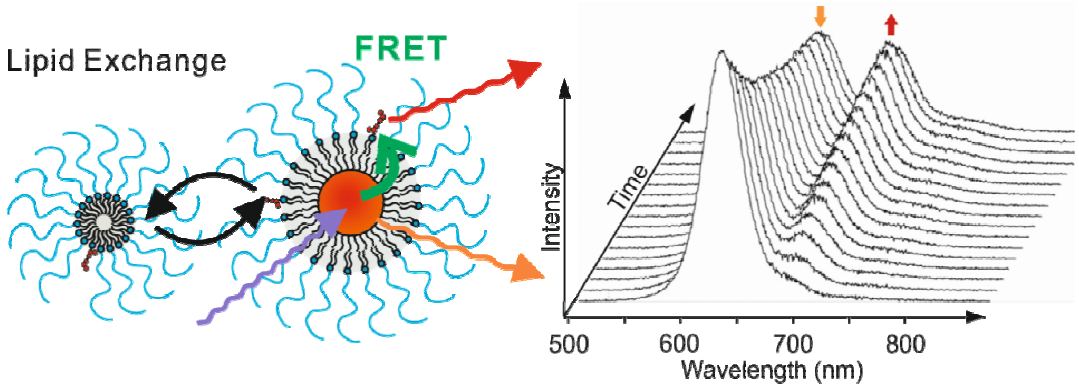

Figure 1. (left) Schematic representation of lipid-exchange between Cy5.5 labeled PEG micelles and quantum dot (QD) micelles , and the Förster resonance energy transfer (FRET) from QD to Cy5.5 lipids. (right) Time dependent emission spectra showing an increase in the dye emission intensity in time due to lipid exchange.

In this presentation we apply the Förster resonance energy transfer (FRET) from quantum dot (QD) core to dye labeled lipids at the surface to monitor the lipid exchange dynamics *in situ* (see Fig. 1) and to study its dependence on concentration, temperature and solvent. A kinetic model is developed to describe the experimental data, to determine the rate constants and the activation energy for lipid exchange. Next, a lipoprotein-based nanoparticle that consists of a QD core and a Cy5.5 labeled lipidic coating is applied to study of lipoprotein interactions, lipid exchange dynamics, and the influence of apolipoproteins on these processes and to exploit FRET to visualize HDL association with macrophage cells[4]. The application of the FRET system was extended to *in vivo* experiments. The distribution, dissociation and fate of different components of the QD - dye lipid micelles was followed in time for our dual

labeled nanoparticle by tuning its optical features (both QD emission and dye emission) to the near-infrared.Through *in vivo* fluorescence imaging techniques, it is shown how the quantum dot core hybrid nanoparticles encounter rapid lipid exchange processes with blood proteins during circulation in the blood stream.

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PET molecular imaging in the evaluation of stem cell therapy

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Being able to self-renew and differentiate into virtually all cell types, both human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSCs) have exciting therapeutic implications for disorders involving irreversible cell loss. When stem cells are used for medical treatments, noninvasive evaluation of transplanted cell and organ function becomes essential. The advent of molecular imaging has led to unprecedented progress in understanding the fundamental behavior of stem cells, including their survival, biodistribution, therapeutic response in the targeted tissues of interest. This lecture summarizes PET molecular imaging technologies and how PET have advanced the current understanding of different stem cell therapies for cerebral ischemia. Molecular imaging could be considered to serve a critical role in stem cell research and the development of future stem cell treatments.

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Ultrasmall Inorganic Nanoparticles for Bioimaging

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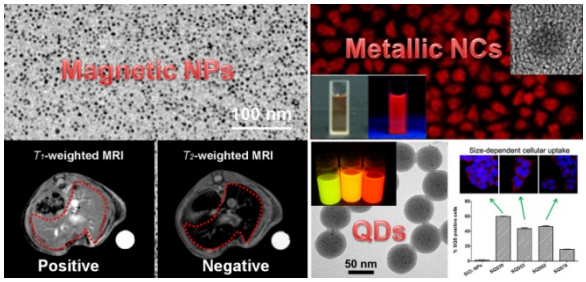
When the size of inorganic particles is reduced to nano scale or sub-nanometer scale, they exhibit novel properties in comparison with their bulk analogues. One example is magnetic iron oxide nanoparticles (MIONs), which show superparamagnetism when their size is below the critical size (e.g. 20 nm for Fe_3O_4 particles) where they turn from ferromagnetic into superparamagnetic.[1, 2] These superparamagnetic MIONs have been extensively used as negative contrast agents for magnetic resonance imaging (MRI) due to their strong magnetization.[3] Further decrease of their size into ultrasmall range (D < 5.0 nm) leads to more suppression in negative enhancement effect than positive enhancement effect in MRI, simultaneously resulting in bright and dark images under T_1- and T_2-weighted MRI conditions.[4-6] Another example is metal nanoparticles which display strong fluorescence when their size is reduced to sub-nanometer.[7-9] These fluorescent metal nanoclusters have shown great potential in cell labeling and imaging as alternatives to fluorescent QDs. Here I will introduce our work (Figure 1) on (i) preparation and application of magnetic iron oxide nanoparticles for MRI;[1-6] (ii) synthesis of ultrasmall metallic nanoclusters for fluorescence labeling and imaging;[7-9] and (iii) preparation of QDs and surface functionalization for cell imaging.[10-12]



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Chemical routes to size-, shape-, and surface-controlled magnetic nanocrystals

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Magnetic nanoparticles based on iron oxides offer great potential to develop applications driven by their unique physical and chemical properties, such as size- and shape-dependent superparamagnetism and the ability to further expand those properties by tuning the surface features. In particular, water-based magnetic colloids represent a versatile platform for the design of effective tools for biomedicine, being active in cancer therapy, tissue imaging and magnetic separation.[1] The structural, morphological and hence magnetic features of the iron oxide nanoparticles must be tuned for optimal perfomance in a given application.[2,3]

In this work, iron oxide nanocrystals have been prepared as prospective heat mediators in magnetic fluid hyperthermia therapy and as negative contrast agents in magnetic resonance imaging. To this end, we compare procedures based on the co-precipitation of Fe(II) and Fe(III) salts in alkaline media and protocols based on the partial oxidation of iron (II) precursors.

The synthesis outcome has been investigated by X-Ray diffraction, Transmission electron microscopy, thermal analysis and dynamic light scattering. It was found that by adjusting the synthetic parameters magnetic iron oxide nanocrystals with either spherical or cubic and cuboctahedral shape were obtained. Procedures for post-synthesis surface modification were also investigated in order to obtain water-based colloids with high nanoparticle concentration and long-term stability. SQUID magnetometry was used to investigate the magnetic properties of the prepared nanostructures. The nanocrystals were tested as hyperthermic mediators through Specific Absorption Rate (SAR) measurements, taking particular care to the optimization of materials for a reproducible temperature kinetic behavior. The efficiency as contrast agents for magnetic resonance imaging was investigated through relaxometric characterization by NMR dispersion curves and by in vivo imaging.

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Acknowledgements

Part of this work has been supported by the Italian Ministry for Education, University and Research (MIUR) through the PRIN 2009 call.

Multifunctional Magnetic Nanoparticles for Targeted Cancer Diagnose and Therapy

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Magnetic nanoparticles, especially hollow magnetic nanopartices, which have controlled size, ability to be remote manipulation, and enhancement of contrast in magnetic resonance imaging (MRI), have been applied as multifunctional probes in biomedical field, including MRI, drug delivery and magnetic hyperthermia.[1] While carbon materials, with high absorption in near-infrared (NIR) optical region, can be used for photoacoustic tomography (PAT) and photothermal therapy (PTT).

In this talk, we will first present hollow manganese phosphate NPs (HMP NPs) with particle size of 18 nm and a 10 nm hollow structure, which were synthesized by a controlled ion transfer process, for pH-modulated cancer cell targeted MRI and drug delivery.[2] Folic acid (FA) was selected as a target molecular for specific binding with cancer cells, and doxorubicin was loaded into the hollow structure for cancer therapy. This multifucntional probe can specifically target cancer cells overexpressing FA receptors, and be engulfed by lysosomes. The HMP NPs were dissolved at low pH environment in lysosomes, which can release Mn^{2+} for sensitive MRI, and DOX loaded for effective killing of cancer cells.[3]

We then talk about Hagg iron carbide nanoparticles (Fe_5C_2 NPs) based materials for bimodal tumor imaging and therapy. The probe exhibits high saturation magnetization, r_2 relaxivity and temperature increasing after exposure to NIR. The conjugation of Herceptin enabled the targeting to Her2-overexpressed cells (SK-OV-3 cells). After incubation with NPs in vitro, SK-OV-3 cells showed much lower MRI T_2 signal, and no noticeable in vitro toxicity has been observed. Determined by using a fluorescent viability stain, cells incubated with NPs and exposed to NIR light were found to have undergone photothermally induced morbidity. The in vivo experiments were carried out on nude mice with ovarian cancer modal. After injection of NPs through the tail vein, it showed long-lasting negative-contrast enhancement MRI as well as high PAT signal at the tumor site. High tumore ablation was achieved after NIR irritation. From the loss of body weight, morphological and pathological examinations, almost no systematic toxicity has been observed. Our results highlight the great potential of Fe_5C_2 NPs as a multifunctional probe for cancer theranostic applications.

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Synchrotron X-ray imaging of nanoparticle fate in biology

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Contrast and composition of nanoparticles can provide opportunity for tracking and labeling for X-ray based imaging techniques. These properties can afford multiple imaging modalities for X-ray based detection, including as contrast agents for radiography and CT, labeling for X-ray fluorescence (XRF) as well as direct imaging of samples for nanoparticle fate in cells and tissues. High resolution, energy tunability and rapid imaging afforded in synchrotron sources have allowed new insights into nanoparticle flow in-vivo, fate and association. This talk overviews several key papers where: nanoparticles have been used for quantifying tumour vasculature in whole animal tumour in 3D[1]; differences in nanoparticle fate between cell lines have been quantified in 3D[2-3]; and using ultra-fast X-ray fluorescence mapping has studied nanoparticle fate in tissues for pharmacokinetic interpretation as well as acted as XRF labels with antibody functionalisation.

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Manganese-based Contrast Agents for Molecular Magnetic Resonance Imaging

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Most available contrast agents for regular and molecular magnetic resonance imaging (MRI) are based on the paramagnetic forms of metal gadolinium (Gd). In recent years, many efforts are also directed to synthesize and evaluate MRI contrast agents based on paramagnetic forms of metal manganese, from divalent ion (Mn^{2+}) to chelate of Mn^{2+}, such as Mn-dipyridoxaldiphosphate (Mn-DPDP), to nanoparticles of manganese-containing oxide. Among all the possible applications of manganese-based contrast agents, the most interesting one, and the one that distinguish them from Gd-based contrast agents, is imaging the structure and function of the brain.

Being an analogue of Ca^{2+}, Mn^{2+} can enter neurons via voltage-gated calcium channels in an activity-dependent way, and be transported antrogradely along the axons. At the same time, Mn^{2+} is a T_1-shortening contrast agent, whose existence in tissue can be measured semi-quantitatively by T_1-weighting MRI or quantitative T_1 mapping. Manganese-enhanced MRI (MEMRI) has been used extensively by neuroscientists to tract neuronal tracts, study the functions of brain nuclei and reveal fine cytoarchitecture[1]. Because of the toxicity of free Mn^{2+}, people have tried to use Mn^{2+}-chelate in place of free Mn^{2+} to study the brain. Mn-DPDP is a clinically approved non-toxic contrast agent, which has been use for clinical hepatic and pancreatic imaging. Once in the body, the chelate releases free Mn^{2+} slowly in exchange with other trans-metal ions such as Zn^{2+}, thus resulting in Mn^{2+}-enhanced contrast in the brain[2]. More recently, manganese-containing nanostructures (e.g., MnO, Mn_3O_4 and MnO@Mn_3O_4 nanoparticles) have been attempted, and most of them show promising properties that warrant their further developments[3-5].

In this presentation, manganese-based MRI contrast agents and their applications in neuroscience researches are reviewed. Our recent progresses in synthesis and evaluation of ultrasmall manganese ferrite nanoparticles are also reported.

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Luciferase reporter system for monitoring endogenous microRNAs

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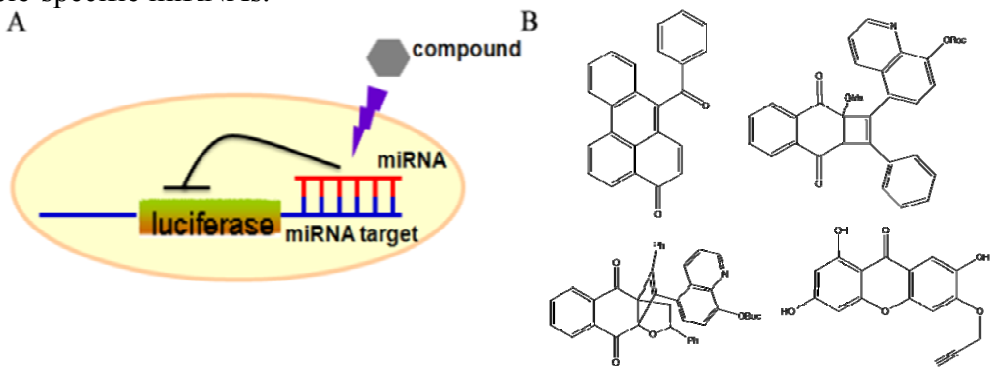
MicroRNAs (miRNAs) are single-stranded non-coding RNAs with the ability to regulate gene expression at post-transcriptional level. Typically, miRNAs function by binding to the 3' untranslated regions (UTR) of target mRNAs, leading to the degradation or repressed expression of target genes.[1] It is estimated that miRNAs are involved in almost every genetic pathway and the regulation of miRNAs plays important roles in physiological and pathological processes. Aberrant expression of miRNAs is associated with the development and progression of many human diseases. Maturation and function of endogenous miRNAs are multi-step processes involving many proteins. Targeting any step in these processes with small molecules could lead to altered expression or function of miRNAs. Therefore unbiased cellular assays have been developed to monitor the alteration of endogenous miRNAs by us.[2] Using transient transfection of luciferase reporter gene with the complementary sequence of various miRNAs of interest, we are able to monitor the alteration on the processing or function of the specific miRNA inside cells that are reflected as the change of luciferase signal from cells. We have screened our compound library based on the cellular reporter systems with luciferase reporter gene to identify different kinds of active molecules, including a universal activator of miRNAs,[3] a universal inhibitor that bearing bio-orthogonal functional groups and a selective inhibitor of muscle-specific miRNAs.



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Application of synchrotron radiation microscopy in the study of the bioeffects of nanomaterials

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Unique physical and chemical properties of nanomaterials make the study of their biological effects face many challenges. Synchrotron radiation is an advanced light source with excellent properties such as high brightness, high collimation, and broad spectrum. Synchrotron based X-ray microscopy imaging technology, with high spatial resolution and good elemental specificity, supplies the study of the interaction between nanoparticles and living systems with a most advanced means. In this paper, we mainly introduced our recent results in this research field. It is indicated that advanced synchrotron based X-ray microscopy techniques are a powerful tool that is capable of precise quantification, and visualization of studying the *in vivo* and *in vitro* biological effects of nanoparticles and their mechanism. In addition, further research direction of this research field is briefly discussed.

Mouse lymphatic endothelial cell targeted probes: anti-LYVE-1 antibody-based magnetic Nanoparticles

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Purpose: To investigate the specific targeting property of lymphatic vessel endothelial hyaluronan receptor-1 binding polyethylene glycol-coated ultrasmall superparamagnetic iron oxide (LYVE-1-PEG-USPIO) nanoparticles to mouse lymphatic endothelial cells (MLECs).
Methods: A ligand specific target to lymphatic vessels was selected by immunohistochemical staining on the sections of a Lewis subcutaneous transplanted tumor. The z-average hydrodynamic diameter (HD), zeta potential, and the relaxivity of PEG-USPIO and LYVE-1-PEG-USPIO nanoparticles were determined with a laser particle analyzer and magnetic resonance T2 spin echo sequence, respectively. Prussian blue staining and transmission electron microscopy (TEM) of nanoparticle labeled cells were performed to determine the nanoparticles' binding form. Magnetic resonance imaging (MRI) was performed in vitro to evaluate the signal enhancement on the T2 spin echo sequence of the nanoparticle labeled cells. The iron content of the labeled cells after the Prussian blue staining and MRI scanning was determined by atomic absorption spectroscopy (AAS).
Results: The anti-LYVE-1 antibody was used as the specific ligand to synthesize the target probe to the MLECs. The mean z-average HDs of the LYVE-1-PEG-USPIO and PEG-USPIO nanoparticles were 57.42 ± 0.31 nm and 47.91 ± 0.73 nm, respectively, and the mean zeta potentials of the LYVE-1-PEG-USPIO and PEG-USPIO nanoparticles were 12.38 ± 4.87 mV and 2.57 ± 0.83 mV, respectively. The relaxivities of the LYVE-1-PEG-USPIO and PEG-USPIO nanoparticles were 185.48 mM-1s-1 and 608.32 mM-1s-1. Cells binding nanoparticles were visualized as blue granules in the Prussian blue staining. The TEM results of the labeled cells showed the specific localization of nanoparticles. The AAS results of labeled cells after the Prussian blue staining and MRI scanning showed that the LYVE-1-PEG-USPIO nanoparticles had good binding selectivity for MLECs. MRI results indicated that the PEG-USPIO and LYVE-1-PEG-USPIO nanoparticles could generate contrast on T2-weighted imaging, and the correlation between R2 and the iron content of the labeled cells was significantly positive.
Conclusion: This study demonstrated that LYVE-1-PEG-USPIO nanoparticles might potentially be used as an MRI contrast agent for targeting MLECs, and the magnetic properties of LYVE-1-PEG-USPIO nanoparticles were suitable for MRI.
*: International Journal of Nanomedicine (Accepted)

Sequentially Light up Cysteine and Homocysteine Based on Kinetic Difference of Probe-Analyte Reactions

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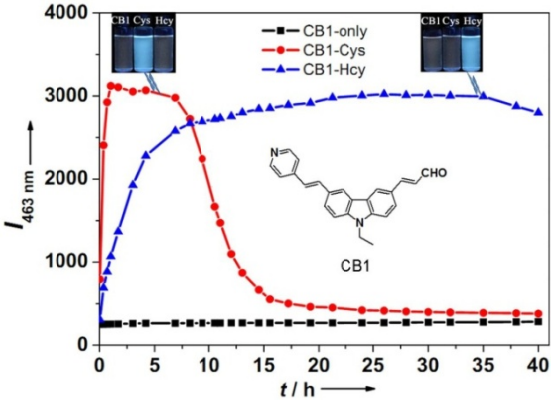
Cysteine (Cys) and homocysteine (Hcy) play different and crucial roles in physiological systems of eukaryotic cells. For example, Cys is an indispensable component in cells as an amine acid of proteins and a precursor of glutathione (GSH). Hcy is an independent risk factor for some severe cardiovascular diseases. The selective detection of Cys over Hcy or *vice versa* is a challenging task because their chemical structures are highly similar to each other. Recently, optical assay based on fluorescent probes becomes an appealing technique owing to its high sensitivity, low cost, real-time *in situ* responses, and potential for *in vivo* imaging of living cells[1-4].

Here, report a novel fluorescent probe for discriminatively detecting Cys and Hcy. This specially designed probe, an *α,β*-unsaturated aldehyde functionalized carbazole derivative (CB**1**), can selectively react with Cys and Hcy to form thiazinane and thiazolidine derivatives in the presence of diverse amino acids and protected Cys. Relying on the evident differences in kinetics, Cys and Hcy can react with the probing molecule in different time windows. The resultants show fluorescence turn-on properties, thus Cys and Hcy are lighted up in a sequential manner (Fig.1).



Probe CB**1** exhibits high selectivity, little interference by pH value and plasma viscosity, and low cell toxicity. Intracellular imaging using both wild-field microscopy (Fig. 2) and two-photon microscope has been achieved. Furthermore, the fluorescence can sustain for more than 40 h. These properties render CB**1** a potential probe for selective imaging Cys/Hcy in living cells.

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Preparation and surface modification of tissue-engineered vascular stents

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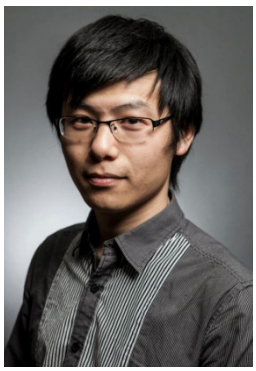
The reconstruction of large bone defects greatly depends on the establishment of a vascular network that temporally precedes new bone formation. Tissue engineering and nanotechnology have enabled nano-composite scaffolds loaded with vascular stents to deal with the current challenges in large bone defects' treatment. In this study, poly(lactic-co-glycolic acid)(PLGA)/nHA vascular stents were fabricated by electrospinning and collagen and heparin sodium were modified to the surface of stents by layer-by-layer electrostatic self-assembly technique. The surface morphology, mechanical strength and anticoagulant property of PLGA/nHA/Col/heparin vascular stents were observed or measured respectively via scanning electron microscopy observation, tensile tests and recalcification time assessment. In addition, bone marrow mesenchymal stem cells (BMSCs) were cultured on these stents and were induced to undergo endothelial differentiation in the presence of vascular endothelial growth factor (VEGF) for antecedent vascularization of tissue engineered bone. The cell-scaffold interactions were analyzed using cell proliferation and SEM. Endothelial differentiation of BMSCs was confirmed via the immunohistochemical staining of platelet endothelial cell adhesion molecules (CD31) and von Willebrand Factor (vWF). These test results proved that the PLGA/nHA/Col/ heparin vascular stent had good surface structures, mechanical properties and biocompatibility. It appears to be a suitable material that can be used in combination with endothelial- differentiated cells to improve vascularization in engineered bone and vascular tissues.

In Vivo Near Infrared FRET Imaging of Nanoparticle Accumulation and Dissociation Kinetics



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In the last decade self-assembled lipidic nanoparticles have been increasingly explored as intravenously injectable agents for biomedical purposes. They can serve as drug delivery vehicles and/or molecular imaging probes. Particularly, lipid-coated inorganic nanocrystals are of great interest as such nanoparticles exhibit unprecedented possibilities with respect to their multifunctionality, potential for derivatization and biocompatibility.[1] Although many lipidic nanoparticles have been developed and applied in vivo for cancer diagnosis and therapy, most studies failed to consider two essential questions: Do these self-assembled particles retain their original composition, and how do they disassemble at and clear from the targeted site? Therefore, an improved understanding of the *in vivo* dynamics of the lipidic nanoparticles and subsequent trafficking of the different nanoparticle components would allow an improved tailoring of nanoparticle design to application.

To this aim, we here introduce a PEG-lipid stabilized nanoparticle that is composed of a near infrared (NIR) quantum dot (QD) core and a NIR dye-lipid corona label (QD-Cy7-PEG).[2] This nanoparticle allowed us to investigate the dynamics of nanoparticle accumulation and dissociation in a tumor mouse model. The large spectra separation between the QD and Cy7-lipid enable us to trace them simultaneously by using an NIR fluorescence imaging system *in vivo*. Moreover, Förster resonance energy transfer (FRET) between the QD core and the Cy7-lipid allowed us to sensitively monitor nanoparticle dissociation. Upon intravenous administration of the nanoparticles, the disassociation process was observed through a decrease of FRET signal in the tumors *in vivo*. *Ex vivo* organ imaging revealed the QD nanocrystal core and the lipid coating to follow different clearance pathways. *In vivo* imaging experiments with mice that received peritumoral injections of QD-Cy7-PEG revealed its trafficking to sentinel lymph nodes. Through fast protein

liquid chromatography analyses of blood plasma, we found the nanoparticle's lipid coating vividly exchanged with plasma proteins as well as lipoproteins.

In conclusion, our study allowed *in vivo* imaging of the accumulation, dissociation and trafficking of lipid-coated nanocrystals. Our technology helps optimizing and tailoring design criteria when using lipid-coated nanocrystals for biomedical purposes in general, and our results warrant caution in the interpretation of imaging data when using them as diagnostic agents specifically.

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Magnetically Engineered Cd-free Quantum Dots as Dual-Modality Probe for Fluorescence/Magnetic Resonance Imaging of Tumors

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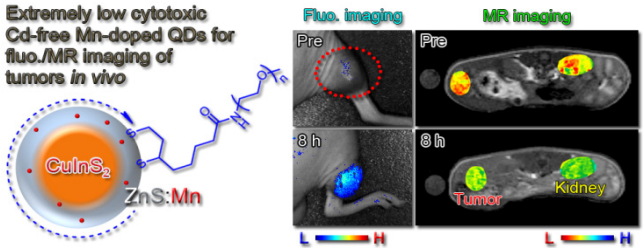

Nanoparticle provides an ideal platform for developing novel fluorescence/ magnetic resonance (MR) dual-modality probes especially for tumor imaging. Herein, magnetically engineered Cd-free $CuInS_2$@ZnS:Mn quantum dots (QDs) were designed, synthesized, and evaluated as potential dual-modality probes for fluorescence and MR imaging of tumors *in vivo*. The synthesis of Mn-doped core-shell structured $CuInS_2$@ZnS mainly comprised three steps, i.e., the preparation of fluorescent $CuInS_2$ seeds, the particle surface coating of ZnS, and the Mn-doping of the ZnS shells. Systematic spectroscopy studies were carried out to illustrate the impacts of ZnS coating and the following Mn-doping on the optical properties of the QDs. In combination with conventional fluorescence, fluorescence excitation, and time-resolved fluorescence measurements, the structure of $CuInS_2$@ZnS:Mn QDs prepared under optimized conditions presented a Zn gradient $CuInS_2$ core and a ZnS outer shell, while Mn ions were mainly located in the ZnS shell, which well balanced the optical and magnetic properties of the resultant QDs. For the following *in vivo* imaging experiments, the hydrophobic $CuInS_2$@ZnS:Mn QDs were transferred into water upon ligand exchange reactions by replacing the 1-dodecanethiol ligand with dihydrolipoic acid-poly(ethylene glycol) (DHLA-PEG) ligand. The MTT assays based on HeLa cells were carried out to evaluate the cytotoxicity of the current Cd-free $CuInS_2$@ZnS:Mn QDs for comparing with that of water soluble CdTe QDs. Further *in vivo* fluorescence and MR imaging experiments suggested that the PEGylated $CuInS_2$@ZnS:Mn QDs could well target both subcutaneous and intraperitoneal tumors *in vivo*.

Facile deposition of continuous gold shell on Tween-20 modified aggregates of Fe_3O_4 nanoparticles

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A facile method to deposit continuous Au shell on Fe_3O_4 aggregates was developed by introducing Tween-20 as surface modification agent to maintain the colloidal stability of the Fe_3O_4 aggregates and provide nucleation and growth sites for Au shell. The Fe_3O_4/Au core-shell particles showed good chemical stability, superparamagnetic properties and efficient photo-thermal conversion performance, which was expected to be a useful material for bio-detection and cancer therapy.

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Surface engineering of gold nanoparticles for *in vitro* siRNA delivery

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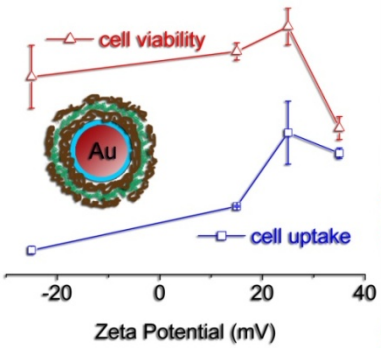
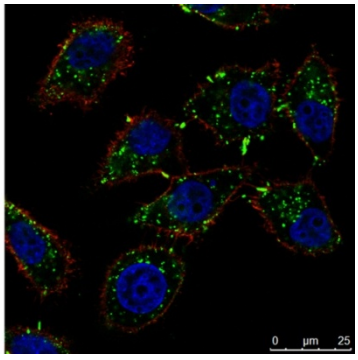
Cellular uptake, endosomal/lysosomal escape, and the effective dissociation from the carrier are a series of hurdles for specific genes to be delivered both *in vitro* and *in vivo*. To construct siRNA delivery systems, poly(allylamine hydrochloride) (PAH) and siRNA were alternately assembled on the surface of Au nanoparticles (GNP), stabilized by denatured bovine serum albumin, by the ionic layer-by-layer (LbL) self-assembly method. By manipulating the outmost PAH layer, GNP–PAH vectors with different surface electric potentials were prepared. Then, the surface potential-dependent cytotoxicity of the resultant GNP–PAH particles was evaluated via sulforhodamine B (SRB) assay, while the surface potential-dependent cellular uptake efficiency was quantitatively analyzed by using the flow cytometry method based on carboxyfluorescein (FAM)-labeled siRNA. It was revealed that the GNP–PAH particles with surface potential of +25 mV exhibited the optimal cellular uptake efficiency and cytotoxicity for human breast cancer MCF-7 cells. Following these results, two more positively charged polyelectrolytes with different protonating abilities in comparison with PAH, *i.e.*, polyethylenimine (PEI), and poly(diallyl dimethyl ammonium chloride) (PDDA), were chosen to fabricate similarly structured vectors. Confocal fluorescence microscopy studies indicated that siRNA delivered by GNP–PAH and GNP–PEI systems was better released than that delivered by the GNP–PDDA system. Further flow cytometric assays based on immunofluorescence staining of the epidermal growth factor receptor (EGFR) revealed that EGFR siRNA delivered by GNP–PAH and GNP–PEI exhibited similar down-regulation effects on EGFR expression in MCF-7 cells. The following dual fluorescence flow cytometry





assays by co-staining phosphatidylserine and DNA suggested the EGFR siRNA delivered by GNP–PAH exhibited an improved silencing effect in comparison with that delivered by the commercial transfection reagent Lipofectamine 2000.

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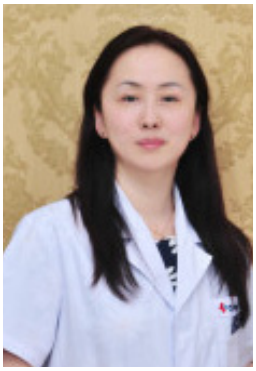
Affibody Modified and Radiolabeled Gold-Iron Oxide Hetero-nanostructures for Tumor PET, Optical and MR Imaging



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A ultrasmall, monodispersed hetero-nanostructure with two different functional nanomaterials (gold (Au) and iron oxide (IO)) within one structure was developed as Affibody based trimodality nanoprobe (positron emission tomography, PET; optical imaging; and magnetic resonance imaging, MRI) for imaging of epidermal growth factor receptor (EGFR) positive tumors. In vitro and in vivo study showed the nanoprobe provided high specificity, sensitivity, and excellent tumor contrast for both PET and MRI imaging in EGFR expressing tumor.

Insight into the Energy Levels of Semiconductor Nanocrystals by a Dopant Approach

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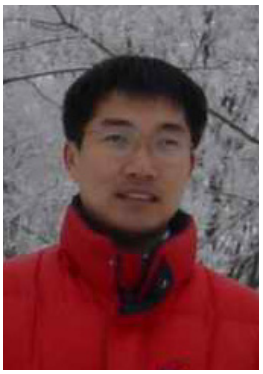

Insight into the energy levels of semiconductor nanocrystals (NCs) is vital important for rational design of nano devices fabricated by using semiconductor NCs as building blocks. In this work, we report an approach for determining the energy levels of NCs by introduction of transition metal dopants. If the energy level of the dopant is located in the forbidden gap of the host NCs, energy levels of the conduction band (CB) of NCs is determinable based on the emission from CB to the dopants, and energy level of the valence band (VB) of NCs is obtainable by using the exciton band gap of NCs to subtract the energy level value of the CB. Through such simple spectral method, the difference in energy levels of different kinds of NCs (CdSe, InP) and the same kind of NCs (CdSe) with different morphologies such as dots, rods and tetrapods can be clearly revealed although they posses the same exciton band gap.

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Ultrasmall Magnetic Nanoparticles for T_1 and T_2 Dual Contrast Magnetic Resonance Imaging

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Magnetic resonance imaging (MRI) is currently one of the most powerful tools for biological molecular imaging and clinical diagnosis [1–2]. Medical diagnosis requires enhanced contrast between normal and pathological tissues, resulting in the development of exogenous MR contrast agents. Most of the presently commercial MR contrast agents are paramagnetic molecular complexes, which are positive (T_1) contrast agents [3]. This kind of contrast agent is limited by their nonspecificity to target, quick removal by renal excretion and short accumulation time in practical applications [4]. Superparamagnetic nanoparticles are another class of MR contrast agents that was normally used as negative (T_2) contrast agents [5-7]. A negative contrast effect and magnetic susceptibility artifacts sometimes restrict their applications in MRI. The development of new types of high-performance nanoparticulate MR contrast agents with either positive (T_1) or dual-contrast (both positive and negative, $T_1 + T_2$) ability is of great importance.

We developed a facile synthesis procedure for ultrasmall PEGylated iron oxide nanoparticles for dual-contrast T_1- and T_2-weighted MRI. The produced superparamagnetic iron oxide nanoparticles (SPIONs) are of high crystallinity and size uniformity with an average diameter of 5.4 nm, and can be individually dispersed in the physiological buffer with high stability. The SPIONs reveal the highest r_1 of 19.7 mM^{-1} s^{-1} and the lowest r_2/r_1 ratio of 2.0 at 1.5 T reported so far for PEGylated iron oxide nanoparticles. T_1- and T_2-weighted MR images showed that the SPIONs could not only improve surrounding water proton signals in the T_1-weighted image, but induce significant signal reduction in the T_2-weighted image. The good contrast effect of the SPIONs as $T_1 + T_2$ dual-contrast agents might be due to its high magnetization, optimal nanoparticle size for $T_1 + T_2$ dual-contrast agents, high size monodispersity and excellent colloidal stability. *In vitro* cell experiments showed that the SPIONs have little effect on HeLa cell viability.

$Mn_xFe_{3-x}O_4$ nanoparticles were also prepared through modifying above preparation procedure of the Fe_3O_4 NPs. By adjusting the reaction conditions, the 'x' value was continuously tuned from 0 to 0.34. The saturation magnetization of the MFNPs gradually increases with increasing Mn^{2+} concentration and reaches to 75.5 emu/g for x=0.34. Careful investigation on the T_1 and T_2 contrast effects of the MFNPs reveals that they present good T_1 and T_2 dual modal MR contrast effects at a magnetic field strength of 3 T when their Fe+Mn concentration is lower than 0.500 mM.

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Gelification: An Effective Measure for Achieving Differently Sized Biocompatible Fe_3O_4 Nanocrystals through a Single Preparation Recipe

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Due to the quantum confinement effect and the nanometer size effect, inorganic nanocrystals exhibit unique particle size-dependent optical, electronic, and magnetic properties compared with their corresponding bulk materials. Although great successes have been achieved over the past decades in the size control of various types of inorganic nanocrystals based on different synthetic principles, developing new synthetic methods and further understanding the mechanisms for delicate control of the particle size remain hot subjects for wet-chemical synthesis of inorganic nanocrystals, especially for magnetic iron oxide nanocrystals due to their bright future in nanomedicine. Following our previous investigations on water-soluble and biocompatible Fe_3O_4 nanocrystals prepared by pyrolyzing $Fe(acac)_3$ in various types of high boiling point solvents,[1–5] recently biocompatible Fe_3O_4 nanocrystals were synthesized through the pyrolysis of ferric acetylacetonate ($Fe(acac)_3$) in diphenyl oxide, in the presence of α,ω-dicarboxyl-terminated polyethylene glycol (HOOC–PEG–COOH) and oleylamine. Unusual gelification phenomena were observed from the aliquots extracted at different reaction stages after they were cooled to room temperature. The average size of the Fe_3O_4 nanocrystals was tuned from 5.8 to 11.7 nm by reaction time with an equilibrium size around 11.3 nm. By increasing the gelification degree of the stock solution, the equilibrium size of the Fe_3O_4 nanocrystals was further increased from 11.3 to 18.9 nm. The underlying gel formation mechanism was investigated and the results suggest that the complexation between HOOC–PEG–COOH and $Fe(acac)_3$, with the help of oleylamine, results in large molecular networks, which are responsible for the gelification of the stock solution, while the interaction between the fragment of the molecular network and Fe_3O_4 nanocrystal is responsible for the second gelification process observed during the early stage of reflux. To further investigate the particle growth behavior, small molecules released during the preparation were collected and analyzed by using photoelectron spectroscopy/photoionization mass spectroscopy (PES/PIMS). It was demonstrated that the pyrolysis of the Fe precursor is strongly correlated with the particle growth process. Further numerical simulations reveal that the first gelification process induced by the complexation between HOOC–PEG–COOH and $Fe(acac)_3$ largely alters the pyrolysis behavior of the Fe precursor; consequently, the equilibrium size of the resultant Fe_3O_4 nanocrystals can effectively be tuned by the gelification degree of the stock solution.

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Wash-free magnetic oligonucleotide probes-based NMR sensor for detecting the Hg ion

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An easily applied and sensitive sensor for the detection of heavy metal ion residues based entirely on magnetic nanoparticle and oligonucleotide was developed. The tool is established on the relaxation of magnetic nanoparticles with different dispersion states. The target analyte, Hg ions, induce the aggregation of the MNP oligonucleotide probes . Accordingly, the light produced by the magnetic relaxation image and the transverse relaxation time (T_2) all change due to the effect of the aggregation. The limit of qualitative detection of the sensor is 0.15 ppt. The recoveries from test samples range between 97.1-101.8%. Using the nuclear resonance instrument, the method is a high throughput and sensitive sensor.

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Tunable Near-Infrared Localized Surface Plasmon Resonance of $Cu_{2-x}S$ Nanocrystals via Incorporation of Zinc Ions

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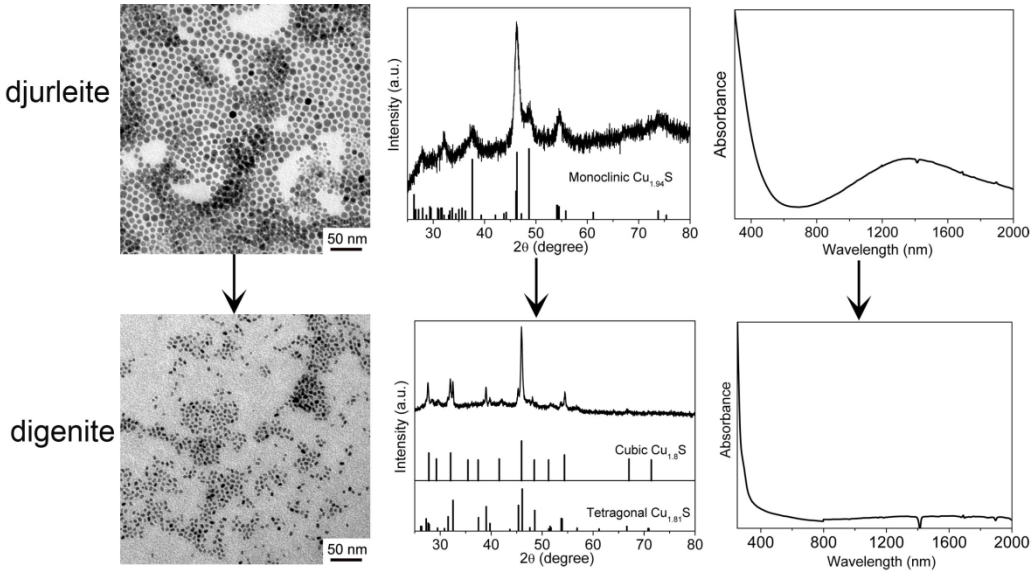
Localized surface Plasmon resonance (LSPR) typically arises from noble metal nanocrystals, which can result in surface-enhanced Raman scattering (SERS). Very recently, LSPR was observed in highly self-doped (or *p*-type) semiconductor nanocrystals, such as cation-deficient $Cu_{2-x}S$, $Cu_{2-x}Se$ and so on[1-3]. Herein, a simple one-pot method has been developed to prepare djurleite ($Cu_{1.94}S$) nanocrystals by direct heating copper acetylacetonate ($Cu(acac)_2$) in *n*-dodecanethiol and a non-coordinating solvent. The as-obtained $Cu_{1.94}S$ nanocrystals exhibit strong LSPR absorption in the near-infrared (NIR) region, indicating the formation of heavily *p*-doped semiconductor nanocrystals. Interestingly, when a small amount of zinc



acetylacetonate ($Zn(acac)_2$) is introduced into the reaction system, the composition of the products evolves from djurleite nanocrystals($Cu_{1.94}S$) to digenite nanocrystals(mixture of $Cu_{1.8}S$ and $Cu_{1.81}S$) as the reaction time is increased. Accompanying the crystal-phase transformation, the morphology is changed from spherical shape to rice-like, which may arise from zinc ions (Zn^{2+}) are incorporated into $Cu_{1.94}S$ lattice. This transformation is closely related with the reaction temperature, reaction time and the amount of $Zn(acac)_2$. As the Zn^{2+} doped into $Cu_{1.94}S$ lattice, the LSPR absorption in the NIR region becomes weaker with increasing dopant concentration, and finally disappears with complete crystal-phase change. This indicates that the as-synthesized nanocrystals is changed from *p*-doped

to *n*-doped semiconductor nanocrystals due to incorporation of Zn^{2+} into $Cu_{2-x}S$ lattice[4].

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Magnetic iron oxide nanoparticles——Tumor detection and BBB transport applications as MRI contrast agent

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Cancer has become the leading killer of human beings worldwide, due to the facts that the clinical management of cancers still suffers from poor efficacies in early tumor detection, metastasis warning, and effective treatment. Ultimately, the effective treatment of cancers not only depends on reliable localization of small malignant tumors, but also needs the molecular information of the tumors. Magnetic iron oxide nanoparticles with unique physical properties and satisfactory safety profile have been used as MRI contrast agent for early tumor detection. In principle, the magnetic iron oxide nanoparticles also provide a platform for further constructing sophisticated multi-functional and/or target-triggering smart probes[1,2]. For the early detection of tumors, we have established the synthesis of iron oxide nanoparticles by using improved thermal decomposition method[3-5]. Biocompatible Fe_3O_4 with tunable sizes were also synthesized under one recipe with the gelification mechanism of the system[6]. Specific cancer detection molecular probes including human colon carcinoma[7] and stomach carcinoma targeting probes were applied for *in vivo* MRI and MRI/SPECT tumor detections[8], respectively.

We also developed a probe based on the iron oxide nanoparticles for blood-brain barrier (BBB) transport detection. Based on the receptor-mediated mechanism, this probe behaves the BBB transporting ability on both in vitro and *in vivo* modal, which provide a potential approach for early MRI detection of brain tumors[9].

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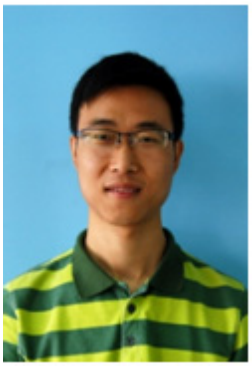
How to visual the Rho GTPase by molecular probes



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RhoGTPases, such as RhoA, RacI and CDC42, act as important intracellular molecular switches cycling between the GDP bound form (inactive) and the GTP bound form (active). They paly important roles in many cell biological processes, and the ability to properly bind and hydrolyze GTP is an essential prerequisite for the maintenance of normal cellular function[1]. It is not surprising that the dysregulation of their activities can result in diverse diseases, including cancer, mental disabilities and neurological diseases[2]. Therefore, the Rho GTPase signaling pathway is always a research hotspot in many disciplines, with the clinical or preclinical goals of targeting them for molecular-targeted therapy of many diseases.

Molecular imaging, especially optical imaging, provides a new platform for noninvasive visualization of biological processes at molecular level in the whole organism. This technique bridges the gap between the identification of biomarkers and their clinical applications. Fluorescence imaging and bioluminescence imaging are being widely used to develop GTPase biosensors, which can noninvasively visualize the activity of Rho GTPases in living subjects.

Fluorescence resonance energy transfer (FRET) is one of the most successful design for fluorescence imaging technology, which depends on the proper spectral overlap of the donor emission and acceptor excitation, the distance between them, and the relative orientation of the fluorophore's transition dipole moments[3]. Itoh and his team used this strategy and developed FRET-based Rho GTPase probes, named "Raichu" probes, to dynamically monitor for the activity of Rac1 and Cdc42 at the membrane during migration in living cells[4]. In these probes, a response unit (a Cdc42- and Rac-binding domain of Pak and Rac1 or Cdc42), was sandwiched by a pair of green fluorescent protein mutants. This response unit can change the spacial conformation and induce FRET between the GDP bound off state and the GTP bound on state. In the next year, the same team further developed another FRET-probes, which can monitor the level of endogenous GTP-RhoA[5]. These biosensors, with high spatial and temoporal resolution, provide insight into the intricate networks. They may promise to resolve important uncertainties or seeming contradictory results in living cells.

On the other hand, Bimolecular Luminescence Complementation (BiLC), as a bioluminescence imaging strategy, has also been used to visualize Rho GTPases. Weibing Leng successfully developed split-luciferase-based genetically encoded

biosensors and demonstrated the robustness through visualizing the three best characterized Rho GTPase (RhoA, Rac1 and CDC42) in living cells and in vivo. The strategy is to reasonably split the gene of firefly luciferase protein into two inactive fragments and then respectively fuse the two fragments to Rho GTPase and the GTPase-binding domain of the specific effector. Upon Rho GTPase interacting with the binding domain in a GTP-dependent manner, these two luciferase fragments are brought into close proximity, leading to luciferase reconstitution and photon production in the presence of the substrate. They also experimentally investigated the sensitivity of these Rho GTPase biosensors to upstream regulatory proteins and extracellular ligands without lysing cells and doing labor-intensive works[6].

Just as a coin has two sides, both of FRET and BiLC have their advantages and disadvantages. The high temporal resolution and spatial resolution enable FRET Rho GTPase probes very suitable for the detection of activities in protrusive areas, such as lamellipodia and filopodia[7]. However, the broader application of these probes may be limited by some disadvantages, such as autofluorescence and challenges of stable expression[8]. Bioluminescence can circumvent cell and tissue auto-luminescence, which results in a better signal to noise ratio for bioluminescent assays[9]. In addition, the enzymatic reaction of luciferase may amplify the minor differences of the signals. On the other side, the BiLC biosensors based on luciferase is also not good at revealing subcellular location. In summary, FRET and BiLC are good supplement to each other. And, along with the development of molecular imaging technology, we can also develop other better molecular probes to visualize these important signal molecules such as Rho GTPases.

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Investigations of the Anchoring Group Effects of PEG ligands on the Relaxivity of Fe_3O_4 Nanoparticles for Achieving High Performance MRI Contrast agents

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Superparamagnetic iron oxide nanoparticles as magnetic resonance imaging (MRI) contrast agents have been intensively investigated over the last two decades.[1-7] To disclose the effects of the anchoring group of surface ligands on the relaxometric properties of Fe_3O_4 nanoparticles, three different types of PEG2000 molecules bearing anchoring groups such as diphosphate, hydroxamate, and catechol, were designed and used to replace the hydrophobic oleate ligands of 3.6 nm and 10.9 nm Fe_3O_4 nanoparticles. Dynamic light scattering studies were carried out for excluding the influence of particle aggregation on the relaxometric behavior of the PEGylated particles. Then, the contrast enhancement properties of the resultant nanoparticles were carefully compared and the related theories were simplified to facilitate the discussion on the impacts of the anchoring group on transverse relaxivity (r_2), longitudinal relaxivity (r_1), and r_2/r_1 ratio. It was found out that the saturated magnetization of the Fe_3O_4 particles, independent of particle size, were closely related to the binding affinity of the anchoring group, so did r_2. In addition, r_2 and r_2/r_1 ratio were strongly correlated with the presence of π-π or *p*-π conjugation structure in the anchoring groups of the PEG ligands. By using PEGylated Fe_3O_4 nanoparticle with optimized T_1 and T_2 contrast effects, a ΔT_1 value of 25% and a ΔT_2 value of 35% were simultaneously achieved in detecting tumors *in vivo*, which manifested the value of the current study for achieving high performance MRI contrast agents.

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The cumulative analysis of promoter methylation alterations by the cationic conjugated polymer-based FRET

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Alterations in the methylation of promoters of cancer-related genes are promising biomarkers for the early detection of disease. Compared with single methylation alteration, assessing combined methylation alterations can provide higher association with specific cancer. Here we use cationic conjugated polymer-based fluorescence resonance energy transfer to quantitatively analyse DNA methylation levels of seven colon cancer-related genes in a Chinese population. Through a stepwise discriminant analysis and cumulative detection of methylation alterations, we acquire high accuracy and sensitivity for colon cancer detection (86.3 and 86.7%) and for differential diagnosis (97.5 and 94%). Moreover, we identify a correlation between the CpG island methylator phenotype and clinically important parameters in patients with colon cancer. The cumulative analysis of promoter methylation alterations by the cationic conjugated polymer-based fluorescence resonance energy transfer may be useful for the screening and differential diagnosis of patients with colon cancer, and for performing clinical correlation analyses.

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Quantitative evaluation of spontaneous plasticity of corticospinal projections after rat spinal cord injuries by in vivo diffusion tensor imaging

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Purpose: To quantitatively evaluate the spontaneous plasticity of corticospinal projections after rat spinal cord hemisection by in vivo DTI and to investigate the correlation between the DTI results and those from behavioral analysis and histological examinations.

Methods: Healthy male SD rats were randomly assigned to 2 groups: (1) sham group (n=6); (2) hemisectione injury group (n=8, at T8 level). All the rats were assessed using an open field rating scale and imaged by 7.0T MR scanner in vivo at 1 day, 3 days, 1 week, 2 weeks, 3 weeks, 4 weeks after operation. Thereafter the animals were euthanized for histological examinations. The MR sequences included RARE T2, RARE T1, and DTI. The MRI data processing were performed using ParaVision, DTI Toolkit and TrackVis software.

Results: T2 images revealed high signal intensity in the lesion from 1 day after injury. On T1 images, the signal changes were not apparent. On diffusion tensor tractography(DTT) images, the fibers were disrupted on the right side of the spinal cord, while they were intact on the other side. Quantitative analysis revealed that the number of DTT fibers at 1 day after spinal cord injuries was lower than that in sham group, and increased slightly at subsequent time points. We calculated the FA and λ1 of the corticospinal tract on both sides and found that the FA and λ1 values prominently decreased on the right side compared to the sham group 1 day after injury and gradually increased throughout the 4 weeks of observation. The FA and λ1 values were slightly decreased after injury with slightly increase thereafter on the other side. Locomotion of the right hindlimb of the injured animals was significantly decreased immediately after injury, with gradual recovery for 4 weeks. Significant correlation was observed between the open field rating scale and the number of DTT fibers and the FA, λ1 values of the right side of the corticospinal tract.

Conclusion: There is spontaneous plasticity of intraspinal circuitry after spinal cord injuries in rat. DTI is an promising tool for monitoring spinal cord injuries and evaluating the effectiveness of its treatment protocols.

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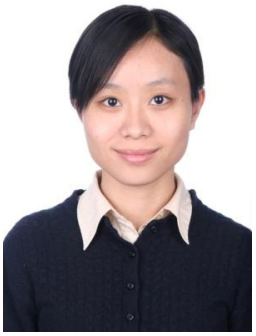
Quantum Dot-Antisense Oligonucleotide Conjugates for Multifunctional Gene Transfection, mRNA Regulation, and Tracking of Biological Processes



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Due to the excellent optical properties, quantum dot (QDs) are greatly desirable for multiplex immunoassays, cellular fluorescence imaging, and in vivo fluorescence imaging[1]. They have also been found to be potentially useful in visually tracking biomolecules inside living cells to elucidate some biological processes at the cellular level. For example, QDs have even been used in recent gene studies[2]. In addition of gene transfection, QD-based gene vectors can successfully be developed for monitoring the cellular uptake of foreign genes. The cellular uptake is undoubtedly one of the most important steps for gene transfection. However, the following endosomal escape, cytoplasmic mobility, and nuclear entry of foreign genes are also very important for in vitro gene transfection with respect to nonviral gene transfection systems. Therefore, to visually track and identify the intracellular localization of a foreign gene would be greatly helpful for revealing the intracellular target sites of the transfected genes, elucidating the biological actions and processes exerted or caused by the transfected genes, and thereby probing the mechanisms of the transfected genes at the cellular level

Through covalently conjugating anti-survivin antisense oligonucleotide (ASON) to thioglycolic acid-capped CdTe QDs via amide bond, we develop a fluorescent system for gene transfection and visually tracking the intracellular behavior of transfected genes[3]. Systematic investigations reveal that negatively charged oligonucleotides covalently conjugated to CdTe QDs can effectively induce the cellular uptake of the still negative CdTe-oligonucleotide conjugates through the macropinocytosis pathway. Further experimental results demonstrate that CdTe-ASON can specifically induce the down-regulation of the survivin mRNA and ultimately induce the apoptosis of HeLa cells. Benefiting from the fluorescence of CdTe QDs, the visualization of the specific localization of the CdTe-ASON is consequently achieved. Systematic results suggest that the perinuclear region is the location where the antisense regulation process occurs. In addition, our researches also reveal that the surface modification of oligonucleotide can effectively suppress the cytotoxicity of the CdTe QDs, which may expand the applications of QDs in cell biology investigations after further improvement.

In summary, our investigations demonstrate that CdTe QDs can not only be used as gene vectors but also offer the possibility of visually tracking the intracellular

localization of a given oligonucleotide, thereby providing the possibilities to correlate the gene functions with their specific intracellular localization.

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The role of Snail in early diagnosis of colorectal cancer metastasis

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Metastasis is the primary obstacle in the treatment of colorectal cancer[1]. Snail is an important regulator of epithelial-mesenchymal transition (EMT) which is a reversible process that often occurs at the invasive front of many metastatic cancers, including colorectal cancer[2,3]. We hypothesized that Snail can be used as an early metastasis marker of colorectal cancer. In this study, we established a reporter gene plasmid which utilizes Snail promoter regulating luciferase expression. We found inflammatory factor Tumor necrosis factor α (TNFα) could up-regulate the transcriptional activity of Snail and then promote colorectal cancer metastasis. Then we established a colorectal cancer cell HCT116-Snail-luc which stably expressed Snail promoter reporter plasmid by use of lentivirus packaging system. Further, a metastasis model in nude mouse was built by injecting HCT116-Snail-luc cells in caudal vein. Next, we injected bacterial lipopolysaccharide (LPS), a byproduct of gramnegative bacteria, into the enterocoelia of mouse to induce tumor metastasis *in vivo*. Using living imaging technique, we found that the activity of Snail was obviously enhanced in those LPS stimulating nude mouse. In summarization, our results illustrated that the activity change of Snail can be used as an early metastasis marker of colorectal cancer.

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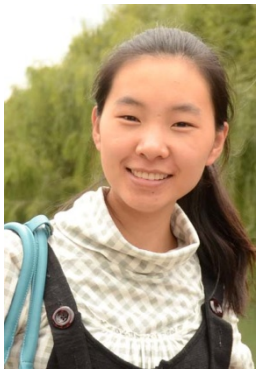
One-Step Continuous Synthesis of Ultrasmall Watersoluble Fe_3O_4 Nanocrystals: Influence of Flow Rate on Saturation Magnetization



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A one-step procedure for the controlled synthesis of highly watersoluble Fe_3O_4 nanocrystals using a continuous flow reactor is presented here. Fe_3O_4 nanocrystals were prepared through pyrolysis of $Fe(acac)_3$ in low boiling point solvent anisole under high pressure (33 bar), with α, ω-dicarboxyl-terminated polyethylene glycol (HOOC-PEG-COOH) and oleylamine as surface ligands. Differently sized ultrasmall Fe_3O_4 nanocrystals (4.8-5.8 nm) were achieved by adjusting the solution flow rate through the reactor. Transmission electron microscopy revealed a relatively narrow size distribution within each sample, and X-ray diffraction analysis showed the produced nanocrystals have high degree of crystallinity. Upon increasing the flow rate, the saturation magnetization of Fe_3O_4 nanocrystals decreased without being directly proportional to the particle size. This procedure provides a labor-saving and reproducible strategy to sufficiently produce watersoluble iron oxide nanocrystals for their emerging biomedical applications.

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Rational design of "smart" aptamers

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Aptamers, are artifical nucleic acid ligands that are evolved from combinatorial nucleic acid libraries by SELEX technique. They have attracted intense research efforts in recent years because of their potential biomedical and analytical applications [1-2]. Given the ease of nucleic acid synthesis and modification, aptamers can be endowed with new properties by molecular engineering.

Through substituting two canonical base pairs of a streptavidin-binding aptamer with T-T mismatched base pairs, we have constructed an Hg^{2+} controlled aptamer, its binding ability is controlled by Hg^{2+} through the formation of T-Hg-T metal base-pairs[3]. The response of this aptamer to Hg^{2+} is sensitive, as low as 50 nM Hg^{2+} can cause significant binding of this aptamer to streptavidin coated beads.

By replacing the stem of the streptavidin-binding aptamer with a split ATP binding aptamer, we tailored a fused aptamer that do not form the binding structure to streptavidin in the absence of ATP. Only ATP can trigger the allosteric change of this aptamer, and result in the restoration of the binding ability to streptavidin. Using streptavidin coated beads to capture the fused aptamer in the presence of ATP and using SYBR-green I as fluorescence indicator, we have developed a label free method for ATP detection.

These strategies of aptamer engineering can extend to construct other aptamers with controllable function. The engineered aptamers hold good potential for applications in many fields, such as signal output control, DNA assembly regulation and smart sensors. As the targets of aptamers are ranging from small molecules, peptide, protein, even to cell and tissue[4], it can be expected that the engineering aptamers will be endowed with various desired functions along with more and more aptamers being generated, such as mimicking a biological response process.

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Activatable Near-Infrared Fluorescent Probe for *In Vivo* Imaging of Fibroblast Activation Protein-alpha

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Fibroblast activation protein-alpha (FAPα) is a cell surface glycoprotein and a member of the serine protease family, which is selectively expressed by tumor-associated fibroblasts in malignant tumors but rarely on normal tissues. FAPα is known as a biomarker of the cancer associated fibroblasts in the stroma, which plays an important role in affecting the proliferation, invasion and metastasis of cancer cells. Besides, FAPα has also been reported to promote tumor growth and invasion and therefore has been of increasing interest as a promising target for designing tumor targeted drugs and imaging agents. Although medicinal study on FAPα inhibitors has led to the discovery of many FAPα-targeting inhibitors including a drug candidate in a phase II clinical trial, the development of imaging probes to monitor the expression and activity of FAPα *in vivo* has largely lagged behind. Herein, we report an activatable near-infrared fluorescent probe (ANP_{FAP}) for *in vivo* optical imaging of FAPα. The ANP_{FAP} consists of a near-infrared dye (Cy5.5) and a quencher dye (QSY21) which are linked together by a short peptide sequence (KGPGPNQC) specific for FAPα cleavage. Because of the efficient fluorescence resonance energy transfer between Cy5.5 and QSY21 in ANP_{FAP}, high contrast on the near-infrared fluorescence signal can be achieved after the cleavage of the peptide sequence by FAPα both *in vitro* and *in vivo*. *In vitro* assay on ANP_{FAP} indicated the specificity and sensitivity of the probe to FAPα. The *in vivo* optical imaging using ANP_{FAP} showed fast tumor uptake as well as high tumor-to-background contrast on U87MG tumor models with FAPα expression, while much lower signal and tumor contrast were observed in the C6 tumor without FAPα expression, demonstrating the *in vivo* targeting specificity of ANP_{FAP}. *Ex vivo* imaging also demonstrated ANP_{FAP} had high tumor uptake at 4 hours post injection. Collectively, these results indicated that ANP_{FAP} could serve as a useful near-infrared optical probe for early detection of FAPα expressing tumors.

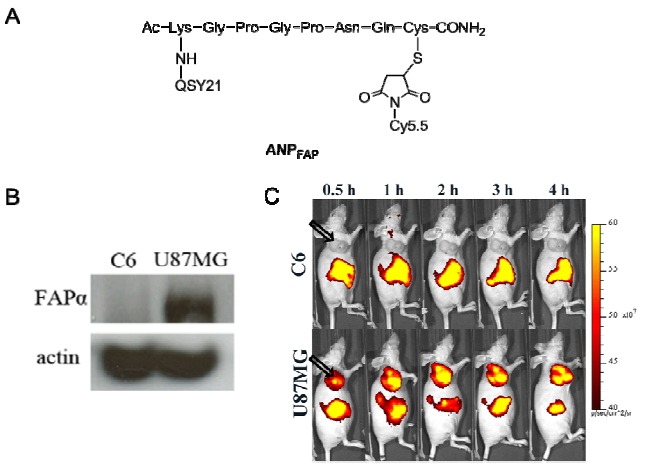

Figure. A) Chemical structure of ANP_{FAP}. B) Protein expression of FAPα in C6 and U87MG tumor tissues. C) Representative *in vivo* fluorescent images of C6 and U87MG tumor-bearing mice at different time points post tail vein injection of ANP_{FAP}.

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$NaGdF_4$ Nanoparticle-Based Molecular Probes for MR Imaging of Intraperitoneal Tumor Xenografts *in vivo*

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Differently sized $NaGdF_4$ nanocrystals with narrow particle size distributions were synthesized by a high temperature approach. Upon ligand exchange, the as-prepared hydrophobic $NaGdF_4$ nanocrystals were transferred into water by using asymmetric PEGs simultaneously bearing phosphate and maleimide groups. Further investigations demonstrated that the water-soluble $NaGdF_4$ nanocrystals, coated by PEG bearing two phosphate groups on the same side, exhibit not only excellent colloidal stability in water and PBS buffer, but also higher T1 relaxivity than Gd-DTPA (Magnevist®). Through "click" reaction between the maleimide residue on particle surface and thiol group from the partly reduced anti-EGFR monoclonal antibody (mAb), $NaGdF_4$-PEG-mAb nanoprobes were constructed and their biocompatibility and binding specificity were evaluated through in vitro experiments. A series of *in vivo* experiments were then carried out for detecting intraperitoneal tumor xenografts in nude mice by using magnetic resonance (MR) imaging technique. The results revealed that the $NaGdF_4$-PEG-mAb probes possessed satisfying tumor-specific targeting ability and strong MR contrast enhancement effects.

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Multimodality imaging assessments of response to metformin therapy for breast cancer

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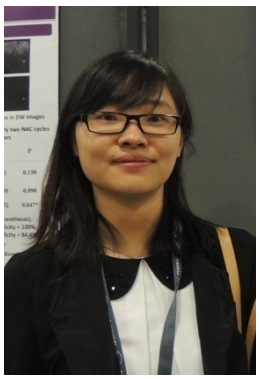


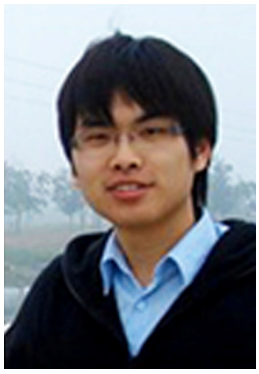
Background Metformin is the most widely used anti-diabetic drug in the world. An increasing body of evidence shows metformin also blocks cell cycle progression and selectively induces apoptosis via caspase activation in some breast tumor cells. Diffusion-weighted imaging (DWI) and bioluminescence imaging (BLI) have great potential in the evaluation of the early response to cancer therapies. We used DWI and BLI in evaluating the response of breast cancer to metformin.

Methods The luciferase-engineered human breast cancer cell line MDA-MB-231 was inoculated into the mammary fat pad of nude mice. Twelve female nude mice bearing tumors were divided into two groups. The mice in the treatment group received metformin (2 mg/ml in drinking water daily) after tumor inoculation, and the mice in the control group were offered drinking water without any drug added. We performed 7T magnetic resonance imaging and optical imaging every week. Imaging included T1- and T2-weighted imaging, DWI, and BLI. After imaging. The tumors were collected and subjected to histological analysis.

Results The mean photons/second of tumors in the treatment group was $(3.00\pm0.43)\times10^6$ at day one, $(1.01\pm0.14)\times10^7$ at 2 weeks, $(5.79\pm1.42)\times10^7$ at 4 weeks, and $(2.33\pm0.70)\times10^7$ at 8 weeks. The mean photons/second of tumors in the control group was $(3.29\pm0.59)\times10^6$ at day one, $(3.59\pm0.63)\times10^7$ at 2 weeks, $(3.87\pm0.56)\times10^8$ at 4 weeks, and $(4.12\pm1.72)\times10^8$ at 8 weeks. Compared to the control group, the treatment group showed an obvious decrease in the mean bioluminescence (photons/s) of the tumors and fewer metastases. Histological examination confirmed the presence of fewer metastases. DWI showed the apparent diffusion coefficient (ADC) value of the tumors; the mean ADC value was $(0.9287\pm0.04346)\times10^{-3}$ mm^2/s in the treated tumors and $(0.7553\pm0.01804)\times10^{-3}$ mm^2/s in the untreated tumors. The ADC value of tumors in the treatment group was significantly higher than the control tumors (P=0.0013).

Conclusions The growth and metastasis of MDA-MB-231 breast cancer may be inhibited by metformin. DWI and BLI have great potentials in the evaluation of the early response to metformin treatment. BLI has a high degree of sensitivity and is able to detect micrometastasis, thus can be used for identifying tumor metastasis *in vivo*.

Bifunctional Superparticles Achieved by Assembling Fluorescent $CuInS_2$@ZnS Quantum Dots and Amphibious Fe_3O_4 Nanocrystals



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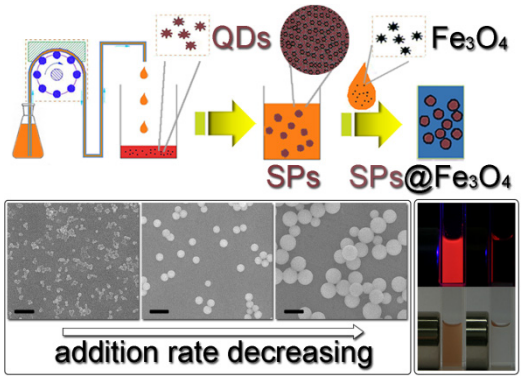
Owing to the remarkable size- and shape-dependent electrical, optical, magnetic, and catalytic properties, inorganic nanocrystals (NCs) are often used as 'artificial atoms' to fabricate colloidal superparticles (SPs), which can magnify the physical properties of single NCs, and exhibit the unique integrated properties because of interactions between the subunits. In order to meet the requirements from the novel advanced functional materials, such as photonics, sensors, catalysis and bioanalysis, the ability to assemble NCs into uniform SPs with precise sizes controlling is increasingly important. Herein, size-tunable SPs with fluorescence and magnetic response were prepared through self-assembling of fluorescent $CuInS_2$@ZnS QDs and amphibious Fe_3O_4 NCs. Systematic analysis suggested that the formation of SPs followed the LaMer model developed for conventional colloidal particles. The ratio of ethanol to cyclohexane (*v*/*v*), R_{EC}, which is regarded as a kind of polarity index could affect the energy barrier against assembling. By manipulating the nucleation and the subsequent growing kinetics through the addition rate of ethanol, the size of the resultant SPs were effectively tuned from 180 nm to 1000 nm simply with narrow size distribution. By over-coating the SPs with amphibious Fe_3O_4 NCs, bi-functional aqueous dispersible SPs were obtained, which thereby provided a method to use amphibious NCs to protect SPs and form multi-functional materials with different properties. These investigations developed a simple method to generate superstructures from NCs by self-assembly which could facilitate the application of nanomaterials.



Lectin-conjugated Fe_2O_3@Au core@shell nanoparticles as dual mode contrast agents for *in vivo* detection of tumor

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Here, we report the covalently conjugation of lectin on Fe_2O_3@Au core@shell nanoparticle (lectin-Fe_2O_3@Au NP) for T_2-weighted magnetic resonance (MR) and X-ray computed tomography (CT) dual-modality imaging. The lectin-Fe_2O_3@Au NPs are prepared by coupling lectins to the Fe_2O_3@Au NP surfaces through bifunctional PEG NHS ester disulfide (NHS-PEG-S-S-PEG-NHS) linkers. After blocked the nonspecific adsorption sites on the nanoparticle surface by thiolated PEG (PEG-SH), the lectin-Fe_2O_3@Au NPs exhibit excellent stability in biological medium and inappreciable cytotoxicity. A series of *in vitro* and *in vivo* experiments were then carried out for evaluating the capabilities of three selected lectin (Con A, RCA and WGA)-Fe_2O_3@Au NPs. The results revealed that the lectin-Fe_2O_3@Au NPs could be used as tumor targeting contrast agents with strong MR/CT contrast enhancement effects.

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Polymer Composite Beads Preparation and Preliminary Application.

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Based on the porous polystyrene microspheres, submicron polystyrene magnetic microspheres have been synthesized by using Fe_3O_4 nanoparticles with different surface modifications as magnetic material. Further magnetic separation experiments by using the immune magnetic macrospheres coated with salmonella specificantibodies showed highly separation efficiency on salmonella samples. Monodisperse magnetic polystyrene microspheres have been successfullysynthesized by adding the iron oxide nanoparticles into the dispersion polymerization reaction systemof preparing porous polystyrene microspheres. PVP and PVP/triethylene glycolcoated iron oxide nanoparticleswere respectively used for the preparation. The magnetic property and colloid stability of acquired magnetic polystyrene microspheres were analyzed. The results showed thatmagnetic polystyrene microspheres by using PVP/triethylene glycolcoated iron oxide nanoparticles as materials were characterized by better magnetic response, which is more suitable for the preparation of immunomagnetic microspheres.Through the electrostatic interaction between magnetic beads andanti-*Salmonella* CSA-1 antibody，submicro immunomagnetic beads were preparedand applied in separating *Salmonella* sp.

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Co-evolution of tumor microenvironment revealed by QDs-based multiplexed imaging

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It has been recognized that cancer is not merely a disease of tumor cells, but a disease of imbalance, in which stromal cells and tumor microenvironment play crucial roles. Extracellular matrix (ECM) as the most abundant component in tumor microenvironment can regulate tumor cells behaviors and tissue tension homeostasis. Collagen makes up the scaffold of tumor microenvironment and affects tumor microenvironment such that it regulates ECM remodeling, characterized by collagen degradation and re-deposition, and promotes tumor associated infiltration, angiogenesis, invasion and migration.

Quantum dots (QDs)-labeled molecular probes are promising platforms to simultaneously study several subtle changes of key biomolecules, because of their unique optical and chemical properties. By using QDs-based imaging technology, several histo-pathological features were revealed by multiplexed QDs imaging of hepatocellular carcinoma: 1) ECM mainly composed of type IV collagen was stiff and less flexible due to the mechanical stress; 2) before being broken, ECM underwent compression and remodeling, accompanied with tumor neo-vessels; 3) ECMB was hydrolyzed at the invasive front, with the remaining prominent linear reorientation of type IV collagen surrounding cancer nests adjacent to neo-vessels. And also, in the study of gastric cancer (GC), we find that there are great differences of tumor macrophages infiltration and angiogenesis between poorly- and well-differentiated GC. Although tumor stroma is less in poorly-differentiated than well-differentiated GC, the “invasion units” consisted of tumor cells, tumor associated macrophages and tumor neo-vessels are much more, and are distributed uniformly across an entire tumor. Typically, they are regarded as single structures scattered throughout the carcinoma, so the “invasion field” consisted of “invasion units” is much stronger. Moreover, in poorly-differentiated adenocarcinoma, single cell migration based on invasion units is the major mode of cancer progression, different from but faster than the collective invasion mode in well-differentiated adenocarcinoma. These features may account for the worse prognosis of poorly-differentiated adenocarcinoma.

In summary, the established approach for QDs-based in situ multiplexed imaging of clinical cancer tissues permits the visualization of the temporal-spatial process of the co-evolution of cancer cells and their microenvironment. Such an approach could help us observe cancer invasion from the perspectives of not only cancer cells but also their microenvironment, gaining new insights into complex and critical cancer event.

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A study focused on gastric cancer stromal microenvironment based on quantum dots labeled molecular probes

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Gastric cancer (GC) invasion and metastasis is determined by the overepression of oncogenes and the activation of typical signal pathways, as well as the interaction between cancer cells and stromal microenvironment, i.e. tumor microenvironment. Considering the clinical oncology issues, this study was designed to evaluate the essential role of tumor microenvironment during the progression of GC by quantum dots (QDs)-based multispectral imaging analysis system.

The new platform based on quantum dots labeled molecular probe and multispectral imaging analysis was established to reveal multiple components *in situ* and simultaneously in the complex tumor microenvironment with high sensitivity and specificity. The new technology revealed a panoramic picture of the tempo-spatial co-evolution of tumor cells and their stroma at the architecture level. In addition, this imaging analysis system could extract spectral information exactly for deeper analysis. With the purpose to promote the theory of GC progression from the perspective of tumor microenvironment, we studied the panoramic picture of the tempo-spatial co-evolution of tumor cells and their stromal. Four patterns of invasion with distinctive cancer cellular stroma interactions were observed, including washing pattern, ameba-like pattern, polarity pattern and linear pattern. Further more, five histopathological properties were suggested by multiplexed QDs imaging. Macrophages infiltration, tumor angiogenesis and ECM remodeling were essential events during the dynamic temporal process. All the results indicated the co-evolution of cancer cells and tumor microenvironment that can not be explained by the variation of only one component.

To translate the new theoretical insights and technique progress into clinical application, the performance of stromal features in GC prognosis was explored. We found that the stromal features performed as well as traditional clinico-pathological features in GC prognosis. High macrophages density, high MVD and low neovessels maturity were unfavorable prognosis factors (P<0.05 for all). Low macrophages density, low MVD and high neovessels maturity were favorable prognosis factors (P<0.05 for all). The integrated information on these components, termed as combined tumor stromal features did better in GC prognosis. In terms of overall lsurviv, the prognostic value of combined tumor stromal features was comparable to traditional clinico-pathological prognosticators. With respect to recurrence, the combined tumor stromal features could have better performance in predicting recurrence risk. All data supported the result that the combined stromal features could open a new field to predict clinical outcome in GC.

In conclusion, QDs-based multiple molecular imaging system highlighted the study about gastric cancer stromal microenvironment, and opened a new field to predict clinical outcome in gastric cancer from the perspectives of tumor microenvironment, which again signified the importance of tumor microenvironment in cancer invasion and metastasis, and call for more intensive explorations in this complex cancer society.

Computer-based Image Studies on Tumor Nests Mathematical Features of Breast Cancer and Their Clinical Prognostic Value

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Breast cancer (BC) is the most common malignant tumor among females in the world. The incidence is still on steady and rapid rising, and increasing number of early BC was diagnosed every year. Currently, Tumor-node-metastasis staging system and WHO histological grading (Scarff-Bloom-Richardson system) are the most widely accepted tools to predict prognosis of BC. However, those two classification systems have inherent defects that may not available to predict the risk of cancer invasion and recurrence accurately and steadily. Therefore, accurately predict the biological behaviors of BC based on the local tumor information still remains a major problem in the clinical diagnosis and treatment of BC.

This study aimed to establish a computer image analysis and processing method to extract mathematical parameters (MPs) of breast IDC TNs, which were labeled with CK by immunohistochemistry. Using the clinical outcome information as the ultimate judgment, the prognostic value of these morphologic features was analyzed.

We have obtained 8 MPs to characterize the size, shape, surface features, spatial closeness and discreteness of TNs. Using 5-DFS as golden criterion to judge their clinical significances, we found 7 out of these 8 parameters of TNs had statistically significant correlation with 5-DFS. ROC analysis showed that number, circularity and total perimeter had area under curve > 0.5. Then we further analyzed the efficiency of these parameters by Cox multivariate analysis, which identified integrated parameter of TNs as an independent prognostic factor for 5-DFS. Therefore, the results suggest mathematical features of cancer cell groups could indeed have important and independent impact on the clinical outcomes of BC patients.

In conclusion, this study demonstrated that mathematic features of TNs morphology could help predict the biological behaviors of breast IDC, and the predictive importance of TNs integrated parameter could be no less than N stage, but no more than histological grading. Therefore, for future work to develop a comprehensive model to predict IDC invasion and metastasis based on information extracted from local tumor itself, the integrated parameter combined TNs number, circularity and total perimeter could be considered as useful candidates to be incorporated into this strategy.

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pH sensitive ratiometricprobe for simultaneously monitoring the intracellular and extracellular pHs

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It is well known that intracellular and extracellular pH plays a key role in many physiological and pathological processes[1].Extracellular pH is known to become lower in tumor microenvironment[2] and in several other physiological events[3]. Sensors that can reveal the pH difference between the intracellular and extracellular regions would be helpful for the studies of cancer and cell biology[4].Probes forsimultaneously monitoring the pH change inside and outside living cells are rarely available. In our work, we describe a new ratiometric pH fluorophorethat was synthesized by condensation of 4-bromine-1, 8-naphthalimides and 3-amino-1, 2, 4-triazole. In the range of pH 5-8,the only N-H in theheterocycle-fused aromatic ring system of this fluorophoreundergoes a reversible deprotonation-protonation process, which results in a largered shiftof the absorption (from yellow to orange)and emissionspectra (from blue to green).In aqueous solution, this fluorophore exhibits good pH selectivity, high photostability,high tolerance to ionic strength,and high fluorescence quantum yield in both the acid and base forms. A long chain derivative of this fluorophore (HNNA) was designed for cellular pH sensing. HNNA was found to locate on the membrane structure of cells, and was successfully used for mapping the pH change in both the extracellularmicroenvironment and the inner cells by confocal imaging.

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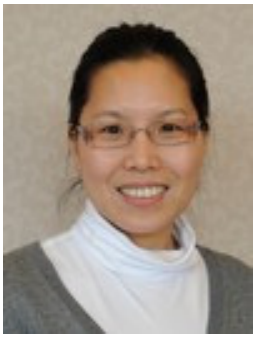
PCR mediated nanoscale magnetic assembled sensor for DNA detection



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An ultrasensitive method for DNA detection based on magnetic assembly induced by polymerase chain reaction (PCR) was developed. The sensor showed a low limit of detection (LOD) of 4.26 aM with a wide range of target DNA from 0.01 fM to 10 000 fM.

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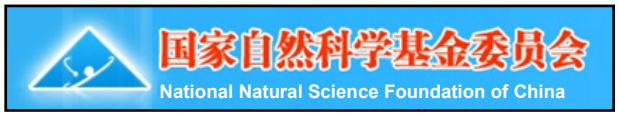
Acknowledgments of Financial Support



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