PROCEEDINGS OF THE 5TH CHINA-JAPAN SYMPOSIUM ON NANOMEDICINE

SEPTEMBER 16-18, 2017

SUZHOU, CHINA

中国科学院苏州纳米技术与纳米仿生研究所

Suzhou Institute of Nano-Tech and Nano-Bionics (SINANO), Chinese Academy of Sciences

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Friendly Reminder

It is our great pleasure to have you to Suzhou in this early autumn to attend the 5th China-Japan Symposium on Nanomedicine, which is sponsored by CAS Key Laboratory of Nano-Bio Interface, Suzhou Institute of Nano-Tech and Nano-Bionics, Chinese Academy of Sciences.

For the comfort and joy of your stay in Suzhou, we would like to offer you some friendly reminders.

1. Hotel and Transportation

The symposium hotel is Jinling Guanyuan International Hotel Suzhou, which is located at No. 168 Cuiwei Street, Suzhou Industrial Park, Jiangsu Province, China.

Please email your trip itinerary and contact information to Ms Caixia Chen at cxchen2010@sinano.ac.cn by Sept. 10. We will arrange pick-up and delivery services between the airport/railway station and the hotel.

2. Conference Registration

2.1 Check-in at Hotel Reception and sign-in at the registration desk.

2.2 Dinner at 18:30 on Sept. 16 at Bauhinia orchid hall on the first floor of the hotel.

3. Meals

3.1 Breakfast is provided in the western food dining hall on the first floor of the hotel. Please gather at the lobby of the hotel to take the bus to the conference hall at 8:00 a.m.

3.2 Lunch (arranged by organizer)

3.3 Dinner (arranged by organizer)

4. Local Organization Committees

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Please feel free to ask for any help from us.

Conference Schedule

Sept.16, 2017 Check-in at the hotel

Sept.17, 2017 Conference at 2nd Floor, Building C of Suzhou Institute of Nano-Tech and Nano-Bionics, CAS

Sept.18, 2017 Conference, tourism and departure

Sept.19, 2017 Departure

Date	Time	Topic	Speaker	Chair
2017.09.17	8:30-8:50	Opening address	Hui Yang, Director of SINANO	Prof. Qiangbin Wang
			Prof. Urisu	
			Prof. Wan	
	8:50-9:10	Noble application of planar-patch-clamp in the field of nano-bio-medicine	Tsuneo Urisu	Prof. Ning Gu
	9:10-9:30	Surface modification with functional molecular patterns revealed by in-situ STM	Lijun Wan	
	9:30-9:50	Development of quantitative evaluation method of protein heterodimers	Narufumi Kitamura	
	9:50-10:10	Near-infrared-II Ag_2S quantum dot-based nanoplatforms for precision cancer therapy	Chunyan Li	
	10:10-10:30	Cell surface engineering for manipulating cell functions	Yusuke Arima	
	10:30-10:50	Tea Break & Group Photos		
	10:50-11:10	Differentiation of mesenchymal stem	Koichi Kato	Prof. Tsuneo

		cells in response to anisotropic microenvironments established in three-dimensional pellets		Urisu
	11:10-11:30	Functional nanoparticles for tumor imaging and therapy	Mingyuan Gao	
	11:30-11:50	The investigation of local dipole moment on TiO_2(110) surface by electrostatic force microscopy	Yan Jun Li	
	11:50-12:10	DOX-loaded magnetic alginate-chitosan microspheres: AMF-triggered chemo-thermal synergistic therapy platform for in-vivo postsurgical treatment of breast cancer	Haiming Fan	
	12:20-14:00	Lunch		
	14:00-14:20	Iron-based nanoparticles for magnetic labeling stem cells	Ning Gu	Prof. Haiyan Xu
	14:20-14:40	Multifunctional organosilica nanoparticles toward theranostics	Michihiro Nakamura	
	14:40-15:00	Gold nanoshell-based system for multiple treatments to EML4-ALK NSCLC	Yueqing Gu	
	15:00-15:20	Second harmonic generation properties for silica coated ZnO particles	Jie Lin	
	15:20-15:40	Biomedical applications of graphene oxide: from drug delivery,	Zhijun Zhang	

		bioimaging, to stem cell regenerative medicine		
	15:40-16:00	Tea Break		
	16:00-16:20	Magnetic nanoparticles for theranostics	Yuko Ichiyanagi	Prof. Koichi Kato
	16:20-16:40	Single-virus tracking with quantum dots: unravelling entry mechanism of influenza A virus	Daiwen Pang	
	16:40-17:00	Preparation of nucleus targeting molecular capsule and its intracellular localization	Keisuke Yoshikiyo	
	17:00-17:20	Inhibitory effects of polymer encapsulated As_4S_4 on chronic myeloid leukemia cells through inducing cell cycle arrest and differentiation	Haiyan Xu	
	17:20-17:40	Peroxidase-like activity of apoferritin paired gold clusters for glucose detection	Li Xu	
	17:40-18:00	Photothermal theranostic nanoprobes in the NIR-II window	Jiang Jiang	
	18:00	Dinner Party		
2017.09.18	08:30-08:50	Applications of Raman spectrometry to cytological diagnosis	Yasuhisa Fujita	Prof. Youqing Shen
	08:50-09:10	DNA hydrogels and their application in 3D bioprinting	Dongsheng Liu	
	09:10-09:30	Bioengineered surface design for mesenchymal stem cell culture	Isao Hirata	
	09:30-09:50	Nanotechnology for	Zhuang Liu	

		innovative cancer imaging and therapy strategies		
	09:50-10:10	High efficient capture and isolation of circulating tumor cells on nano-bio interfaces	Renjun Pei	
	10:10-10:40	Tea Break		
	10:40-11:00	TiO_2 nanoparticles-based nanomedicine for sonodynamic therapy	Atsushi Harada	Prof. Daiwen Pang
	11:00-11:20	Molecular engineering of polymers for cancer nanomedicine	Youqing Shen	
	11:20-11:40	Strategies to enhance the siRNA delivery efficiency of non-virus carriers	Jian Liu	
	11:40-12:00	Soft plasmonic nanomembrane as surface-attachable SERS substrates with high signal uniformity	Yi Chen	
	12:00-12:10	Closing remarks by Prof. Kato and Prof. Gu		Prof. Qiangbin Wang
	12:15-13:00	Lunch		
	13:00-18:00	Tourism Tongli Ancient Town		
	18:00	Dinner		
2017.09.19	The hotel check out and departure			

List of Participants

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Abstracts

Noble application of planar-patch-clamp in the field of nano-bio-medicine

Tsuneo Urisu[1], Zhi-Hong Wang[1], Hidetaka Uno[1], Yuko Kurita[1], Shinsuke Ishigaki[2], Yuzuru Takamura[3]

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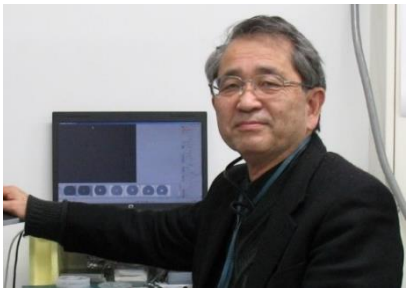
Invention of incubation type planar patch clamp [1] has opened noble applications of planar patch clamp in the field of nano-bio-medicine. By using a salt bridge type stable electrode, the base line noise of the neuronal network ion-channel current measurements has been drastically decreased, and enaboled the channel current measurements with the neuronal network after long time incubations. The planar patch clamp chip having cell cage structures on the surface can form the neuronal network keeping a neuron cell soma on the micropore of the chip. Significant cost cutting by using the Si microfablication technology made a practical use of neuronal network high throughput screening device with something real. We are now developing the technology of cell seeding inside of many cell cages selectively. Since the in vitro neuronal network is extremely complex, to realize the practical use of the neuronal network high throughput screening device, it is also important to make clear the role of the interneurons in the function of the in vitro neuronal network.

Recently we have successfully developed another noble application of the planar patch clamp in the field of nano-bio-medicine. That is the single cell analysis using the planar patch clamp. Single HEK 293 cell was trapped on the micro-pore of the patch clamp chip, and cell membrane contacting the micropore was broken by the suction from the back side of the micropore and the cytoplasm solution was extracted. The mRNA contained in the extracted solution was successfully analysed by the real time PCR after the reverse transcription of the mRNA.

Reference
1. T. Urisu et al., Analytical and Bioanalytical Chemistry, 391 (2008) 2703-2709.

Tsuneo Urisu



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Surface modification with functional molecular patterns revealed by in-situ STM

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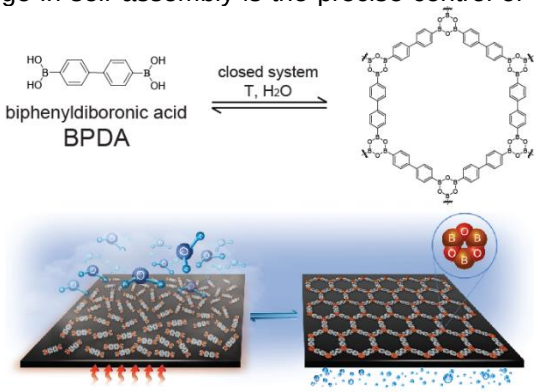
For biochemical research and bio-device fabrication, modifying a solid surface by molecular patterns, adsorption and regular dispersion of biomolecules are important issues, which can be realized by nanoscience and nanotechnology, especially by molecular engineering [1]. As a result of intensive study, self-assembly is a promising strategy for modifying and constructing molecular nanostructures on a surface. A challenge in self-assembly is the precise control of nanostructure and arrangement of molecules. In this presentation, molecular structures on different substrates such as Au (111) and HOPG are reported. The structures are investigated by scanning tunneling microscopy (STM) in ambient and electrolyte solution. The adsorbed molecules can form well-defined molecular assembly with different symmetries. The assembly with the individual molecules could also be polymerized into molecular nanowires and nanonetworks, schematically shown in the right figure [2-4]. Biomolecules can be deposit in the cavity of the network. The modified surface shows potential in biomolecule research and bio-device fabrication.



References:
1. Li-Jun Wan, Acc. Chem. Res., 39(2006)334.
2. R. Wen, G. B. Pan, Li-Jun Wan, J. Am. Chem. Soc., 130(2008)12123.
3. Jia Liu, Xin Deng, Dong Wang, Li-Jun Wan, J. Am. Chem. Soc., 133(2011)21010.
4. Xuan-He Liu, Cui-Zhong Guan, San-Yuan Ding, Wei Wang, Hui-Juan Yan, Dong Wang, Li-Jun Wan, J. Am. Chem. Soc.,135(2013)10470.

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Development of quantitative evaluation method of protein heterodimers

Narufumi Kitamura[1], Hiroshi Tada[2], Kohsuke Gonda[1]

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Protein-protein interaction, especially heterodimerizaion, plays an important role in cellular signaling pathways that control cell proliferation, motility and survival. The members of human epidermal growth factor receptor (HER) family are overexpressed on many kinds of human cancer cells and play a pivotal role for cancer progression. Activation of HER family protein is triggered by their dimerization. Many researchers in this field recently focus on diagnosis of homo- or hetero-dimmers of HER family with quantitative sensitivity. These studies revealed that the formation of HER2/HER3 hetero-dimer was the most potent signaling pair in HER2 positive breast cancer, leading to proliferation, angiogenesis, and metastasis. However, previous developments of imaging of HER2/HER3 heterodimers did not achieve the level of clinical application.

In this study, we developed a new method, fluorescence particle-to-particle energy transfer, for quantitative evaluation of HER2/HER3 heterodimers. Two kinds of fluorescent nanoparticles, quantum dots (QDs) and phosphor integrated dots (PIDs) [1], were prepared as a pair of fluorescent probes. Antibodies which could be targeted to intracellular domain of HER2 and HER3 were selected. We performed detecting HER2/HER3 hetero-dimers by using QDs as energy donor and PIDs as energy acceptor which induce fluorescence particle-to-particle energy transfer. As the efficiency of fluorescence energy transfer is extremely sensitive to the distance between the pair of particles. Therefore, only in the case of heterodimer formed, energy transfer based fluorescence can be detected. In addition, we focused on the phenomena which single-particle of QD shows fluorescence intermittency, called ‘blinking’. Basically, the fluorescence of PID is not intermittency but continuous. However, the fluorescence of PID which is excited by the energy from QD reflects blinking of donor particle. We applied single-particle analysis [2] to energy transfer based PID-fluorescence for quantitative evaluation of HER2/HER3 heterodimers on breast cancer cell lines.

Reference
1. Gonda K. et al. Scientific Reports.2017; 7: 7509.
2. Miyashita M., Gonda K. et al. Cancer Med.2016; 5(10): 2813.

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Near-infrared-II Ag_2S quantum dot-based nanoplatforms for precision cancer therapy

Chunyan Li, Yejun Zhang, Guangcun Chen and Qiangbin Wang*.

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Fluorescence imaging in the second near-infrared region (NIR-II, 1000–1700 nm) is more desirable than visible (450–700 nm) and traditional NIR-I imaging (700–950 nm) owing to greatly reduced photon absorption and scattering by tissues, as well as negligible tissue autofluorescence, which promises high-fidelity imaging of deeper tissues and organs. Herein, for the first time, we developed a new type of NIR-II Ag_2S QDs and built novel NIR-II fluorescence imaging systems. Based on this emerging imaging technology, the tissue penetration depth can reach 1.5 cm, and the spatial and temporal resolution of the in vivo imaging can down to 25 μm and 50 ms, respectively. With the advanced NIR-II fluorescence of Ag_2S QDs, high signal to noise ratio imaging of tumor growth, angiogenesis, metastasis and imaging-guided targeting drug-delivery and therapeutics, etc, have been achieved.

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Dr. Chunyan Li received his PhD degree majoring in biochemistry from Fudan University in 2012. Then, he joined SINANO as an assistant professor focusing on the synthesis and applications of NIR-II fluorescence nanoprobes. He is currently an associate professor and his research interests involve NIR and multifunctional nanomaterials for bioimaging and drug delivery.

Cell surface engineering for manipulating cell functions

Yusuke Arima

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Cell behavior is regulated by its microenvironment, including interactions with soluble factors, extracellular matrix substrates, and neighboring cells. It is important to understand and control the cell microenvironment in order to develop methods for tissue engineering and the expansion or differentiation of stem cells. In order to realize cell therapy, it is also crucial to control biological responses against transplanted cells. Engineering surface of cells with natural and synthetic molecules has attracted attention for biomedical applications such as cell therapy and construction of multicellular aggregates.

We have used poly (ethylene glycol) conjugated to a terminal phospholipid (PEG-lipid) for cell surface engineering. The lipid moiety is inserted in the lipid bilayer of living cells through hydrophobic interaction. Conjugation of PEG-lipids with biomolecules (DNA, protein, peptide) allows for their display on cell surface. For example, PEG-lipids carrying single-stranded DNA (ssDNA-PEG-lipid) can modify cell surface with ssDNA. The complementary ssDNA' is used as an artificial glue to attach molecules of interests. This allows for modification of cell surface with biomolecules and nanoparticles, and for attachment of cells to either substrates or different cells, all of which carry the complementary ssDNA'. Taking advantages of wide variety of DNA sequences, we also realized cell attachment to substrate in a spatially controlled manner (cell patterning) and programmed multicellular assembly and disassembly. Recently, we employed supported lipid bilayer formed on glass as a model cell membrane to study biophysical aspects of cell-cell attachment induced by ssDNA-PEG-lipid. In this talk, I will present cell surface engineering using PEG-lipids and its biomedical applications.

This work was supported by a Grant-in-Aid for Scientific Research on Innovative Areas "Nanomedicine Molecular Science" (No. 2306) and for Scientific Research (17H01579) from the Ministry of Education, Culture, Sports, Science, and Technology (MEXT) and by the Center of Innovation Program from MEXT and Japan Science and Technology Agency.

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Differentiation of mesenchymal stem cells in response to anisotropic microenvironments established in three-dimensional pellets

Try Ky[1], Malina Prak[1,2], Isao Hirata[1], and Koichi Kato[1]

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Introduction: Human bone marrow-derived mesenchymal stem cells (MSCs) are considered to be promising as cell sources for cartilage regeneration. However, differentiation of MSCs into chondrocytes can ultimately lead to hypertrophic chondrocytes which later contribute to the calcification of the tissue. Therefore, the suppression of hypertrophic chondrocyte differentiation must be carefully taken into consideration for cartilage regeneration. This study aimed at studying the effect of various conditions in three-dimensional (3D) pellet culture of MSCs on the promotion of chondrogenic differentiation and also the prevention of hypertrophic chondrocyte conversion.

Materials and Methods: MSCs cultured in growth or chondrogenic medium were centrifuged to obtain a pellet. Then, the pellet was cultured under growth medium or chondrogenic medium for up to 28 days. To analyze chondrogenic differentiation, pellets were sliced and stained with H.E and toluidine blue. or immunologically stained to detect HIF-1α (hypoxia marker) and type X collagen (hypertrophic chondrocyte marker). Necrotic and apoptotic cells were analyzed by PI staining and TUNEL assay, respectively. Quantitative PCR was performed to analyze the expression of chondrogenic markers (Sox9 and type II collagen) and mitochondrial redox carriers.

Results and Discussion: Our results demonstrated that chondrocyte consumes less oxygen than that of hBMSCs. Since chondrocyte and hBMSCs consume oxygen at different rate, oxygen gradient and oxygen consumption influence cell necrosis and chondrogenic differentiation in the pellets. HIF-1α, known as a transcription factor that binds to Sox9 promotor to induce chondrogenesis, while impairs the expression of several proteins forming mitochondrial redox carriers, seems to play a key role in chondrogenic differentiation and cell necrosis in 3D pellets. It was further shown that hypertrophic chondrocyte conversion can be suppressed in a medium at low glucose concentration. Accordingly, it may be concluded that MSCs differentiate into chondrocytes in response to anisotropic microenvironments established in a 3D pellet. Pre-chondrogenic differentiation with low glucose concentration may provide optimal conditions for the formation and stabilization of early chondrocytes.

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Functional nanoparticles for tumor imaging and therapy

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Through either passive or active targeting, functional nanoparticles have shown great potentials in tumor diagnosis and therapy. We have spent years' efforts to develop functional nanoparticles and nanoparticle-based probes for imaging of tiny tumors and lymphatic micrometastasis, visualizing of tumor microenvironment abnormal signatures, and tumor photothermal therapies as well. In this presentation, we will present our recent results about tumor theranostic applications of functional nanoparticles.

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Personal History

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The investigation of local dipole moment on TiO_2(110) surface by electrostatic force microscopy

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Au/TiO_2(110) surfaces display extremely high catalytic reactivity [1]. There are many representative models that explain the emerging catalytic activity of Au nanoclusters. It is widely accepted that the perimeter interface of Au/TiO_2 is the reaction site for CO oxidation. However, the injection/extraction mechanism of electrons and the reaction process are not clarified by a comprehensive experimental description. In this study, we proposed a new method to simultaneously measuring topography, local contact potential difference (LCPD) and dipole moment distribution on TiO_2(110) surface.

In the experiment, the DC bias added with ac bias voltage is applied between the tip and sample. Three lock-in amplifiers are used to detect frequency shift of f_m, f_{2m} and f_{3m}. The contact potential difference is numerically calculated from the divided result of f_m and f_{2m} signals [2, 3] and dipole moment is obtained from frequency shift of f_{3m}. We simultaneously measure the topography, LCPD and dipole moment images on TiO_2(110) surface. The details will be reported in the meeting.

References:

1. M. Haruta. Catal. *Today*. **36**, 153-166, 1997.
2. L. L. Kou, Y. J. Li, and Y. Sugawara. *Nanotechnology*. **26**, 195701, 2015.
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DOX-loaded magnetic alginate-chitosan microspheres: AMF-triggered chemo-thermal synergistic therapy platform for in-vivo postsurgical treatment of breast cancer

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DOX-loaded magnetic alginate-chitosan microspheres (DM-ACMSs) were developed as a model system to evaluate alternating magnetic field (AMF)-responsive, chemo-thermal synergistic therapy for multimodality postsurgical treatment of breast cancer. This multimodality function can be achieved by the combination of DOX for chemotherapy, with superparamagnetic iron oxide nanoparticles (SPIONs) as magnetic hyperthermia agents and drug release trigger. Both moieties are encapsulated in alginate-chitosan microspheres which also allow on-demand drug release. It is demonstrated that the optimized SPIONs content in DM-ACMSs is about 0.29 mg/mL Fe, at which DM-ACMSs could exhibit the best hyperthermia performance. Under a remote AMF, DM-ACMSs can exhibit a multi-step, on-off switchable drug release behavior. These DM-ACMs can quickly reach a 22.5% cumulative drug release in tumor site within 10 min upon exposure under AMF, whereas only 0.2% DOX is released in the absence of AMF. Furthermore, a comparison study of AMF and water bath as heating source indicates that the cumulative drug release amount upon AMF exposure is twice of that by water bath heating. Further analysis revealed that the AMF triggered drug release is driven by both thermal and concentration gradient from inside to outside, which can be well-described by the coupling mechanism of mass and heat transfer using Soret diffusion model. In vitro cytotoxicity tests on MCF-7 breast cancer cells shows that the combined therapy based on DM-ACMSs leads to 95.5% cell death, about 1.5-fold and 1.1-fold higher than that of single magnetic hyperthermia or chemotherapy. In vivo anti-tumor effect on tumor-bearing mice demonstrates that the residual tumor disappears in 12 days after chemo-thermal synergistic treatment using DM-ACMSs, and there is no recurrence in entire experiment period (40 days) as compared to 25 days recurrence for single-modality treatment. Our results not only provide an innovative DM-ACMSs system as stimuli-responsive, synergistic chemo-thermal therapy platform for efficient reduction in the recurrence and metastasis of breast cancer, but also gain insight into the intricate interplay of the functional components in magnetic hydrogel microspheres. Hence this work highlights the importance of designing high-performance multimodality therapy platform for future tumor treatment.

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Iron-based nanoparticles for magnetic labeling stem cells

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Stem cells have been regarded as the main hope of cell therapy in medicine. During the realizing clinical application, it is still unclear the origin of stem cells differentiation, growth, and accumulation Thus, exploring the suitable technologies for tracing stem cell in vivo, for instance iron-based nanoparticles in combination with magnetic resonance imaging (MRI), will play a vital role. This presentation will look back the recent progresses on different ways for magnetic labeling stem cell, the metabolism of magnetic substances and the impact on cell systematically. Our preliminary results involving the iron oxide nanoparticles used to label mesenchymal stem cells and the related experiment of small animas will be shown.

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Multifunctional organosilica nanoparticles toward theranostics

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An application of silica nanoparticles to nanomedicine is envisioned to be one of the most important subjects. Novel type of silica nanoparticles, organosilica nanoparticles are both structurally and functionally different from typical silica nanoparticles (inorganosilica nanoparticles) prepared from tetraethoxyorthosilicate [1]. The organosilica nanoparticles contain both interior and exterior functionalities such as mercaptopropyl residue. The organosilica nanoparticles allow for facile surface and internal functionalization, offering new opportunities to create multifunctionalized nanoparticles. In addition, functional fusions of organosilica nanoparticles and other functional nanoparticles such as quantum dots and iron oxides are possible based on organosilica particles technology [3]. Multifunctionalizedorganosilica nanoparticles have high potential to create novel imaging systems and provide novel information of cell characteristics and functions [3]. Multifunctionalizedorganosilica nanoparticles were applied to multimodal imaging and theranosticsdevelopement. The multimodal organosilica nanoparticles containing magnet nanoparticles and fluorescent dye showed new approach to evaluate pathological imaging and advantages of multimodal imaging using MRI and mesoscopic fluorescence imaging. The organosilica nanoparticles containing near-infrared (NIR) dye could detect tumor. NIR light irradiation to tumor tissue improved particles accumulation and reduced tumor tissue due to photodynamic/photothermal effect.

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Gold nanoshell-based system for multiple treatments to EML4-ALK NSCLC

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The gold nanoshell based drug delivery system was established to achieve the combination of gene therapy, chemotherapy and thermal therapy for the treatment of EML4-ALK genefusion NSCLC. Both the ALK and microRNA-301 gene were silent by siRNA sequences. Releases of the siRNA and chemotherapy drug DOX from the nanoshell were triggered upon the irradiation of near-infrared laser, which also provides efficient endosomal escape within the cell by the photo-thermal effect. In vitro and in vivo results indicated the treatment effect of EML4-ALK NSCLC by the nanoshell based system is better than any single treatment. Meanwhile, the drug delivery system exhibited the well property such as stability, tumor targeting ability and sequence protected ability. Further, it was found that the attachment of siRNA on the surface of nanoshell promoted the DOX absorption and loading capacity. The multiple combined treatment based on the gold nanoshell showed great prospect in application.

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Second harmonic generation properties for silica coated ZnO particles

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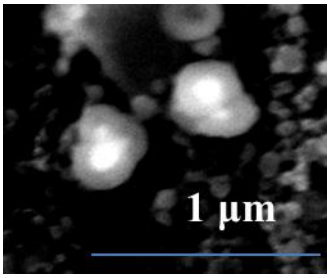
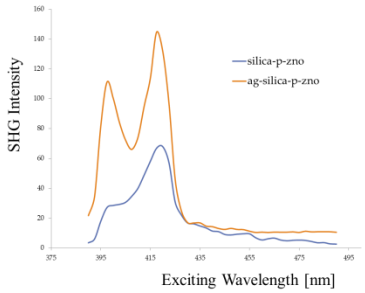
Silica capping attracted more and more interest due to their good environmental compatibility with different materials and surface states modification. Silica coating technique was used to improve the stability and increase the dispensability for ZnO nanostructures which were synthesized using arc-vapor method, therefore to enable the more wide applications. The defects and impurity on the surface of ZnO nanocrystals can be modified to optimize the nonlinear optical properties for bioimaging with no auto-fluorescence above 780 nm and minimal auto-fluorescence below 780 nm. SHG imaging can improve the quality for deep tissue due to the longer penetration depth. Also the infrared excitation reduced the absorption and scattering of optical signal. To achieve high quality tracking and imaging for selective cells for using ZnO second harmonic generation, the SHG conversion efficiency had improved by localized surface plasmonic effects with the excitation of femtosecond laser source ranging in near-infrared from 780-980 nm.

Highly efficient second harmonic signals over a wide range of near-infrared wavelengths, spanning from 780 nm-980 nm, has been observed and can be used in biological imaging. The use of further high energy excitation ranging from 700 nm-755 nm leads to two-photon absorption and yields broadband two photon emissions extending from the 370 nm-450 nm wavelength regime which can be useful for therapeutic applications.





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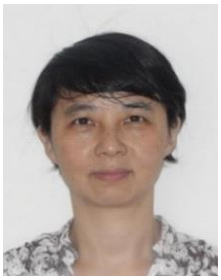

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Biomedical applications of graphene oxide: from drug delivery, bioimaging, to stem cell regenerative medicine

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My talk includes the following topics: (1) Development of graphene oxide (GO)-based nanovectors for controlled loading and targeted delivery of multiple anticancer drugs to overcome multidrug resistance. We have demonstrated that folic acid-modified GO loaded with two anticancer drugs, DOX and CPT, shows specific targeting to MCF-7 cancer cells, and remarkably high cytotoxicity compared to GO loaded with only one drug. (2) Development of GO-based theranostic nanoplatforms for efficient and simultaneous cancer imaging and therapy. I will introduce briefly our recent work on cancer targeted multimodal theranostics. (3) Development of GO-doped or coated scaffolds for stem cell growth, proliferation and differentiation. Our work has demonstrated that doping of GO into PLGA scaffolds not only promotes the attachment and proliferation of hMSCs, but also enhance the hMSCs differentiation toward osteoblast, which may find potential applications in tissue engineering and regenerative medicine.

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Magnetic nanoparticles for theranostics

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Magnetic nanoparticles have drawn attention as they have potential applications for not only recording electric materials but also in the biomedical field such as purification, drug delivery system, diagnostics and hyperthermia treatment. Previously, we obtained monodispersive magnetic nanoparticles (MNPs) by an original wet chemical method, and reported magnetic, structural and thermal properties. Then we have functionalized our magnetic nanoparticles by attaching functional groups. These functional MNPs were further introduced into cells. Furthermore, cancer cell selective MNPs were developed. Based on these techniques, we proposed a therapeutic method of magnetic hyperthermia. The relationship between magnetization and heat dissipation was estimated.

We have carried out in vitro experiment using cultured human breast cancer cells, and drastic hyperthermia effect was observed. We are then proposing development of magnetic nanoparticles for diagnostic and therapeutic materials simultaneously, namely theranostics recently.

Imaging method is one of the effective way for diagnostics. T2 relaxation curves in magnetic resonance (MR) signal measurement were obtained by spin eco sequence for the same magnetic nanoparticles. T2 shortening capability and phantom images of magnetic nanoparticles were examined as an agent of MR imaging. A very high contrast was observed using our MNPs than conventional reagent materials of iron oxides in even short repetition time of TR. Mass spectrometric imaging and CT imaging were also examined as diagnostics applications.

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Single-virus tracking with quantum dots: unravelling entry mechanism of influenza A virus

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Entry is the first critical step for the infection of influenza A virus and of great significance for the research and development of anti-flu drugs. Generally speaking, influenza A virus depends on exploitation of cellular endocytosis to enter its host cells, and how are the details for its entry behaviors? Is there any other route for the virus to enter its host cells besides the endocytosis? With the aid of single-virus tracking technique and quantum dots, we have realized real-time and multi-color visualization of the endocytic process of individual viruses and comprehensive dissection of two distinct dynamin-dependent endocytic pathways of influenza A virus, either dependent on clathrin or not. Based on the sequential progression of protein recruitment and viral motility, we have revealed the asynchronization in the recruitments of clathrin and dynamin during clathrin-dependent entry of virus, with a large population of events for short-lived recruitments of these two proteins being abortive. In addition, the involvement of autophagy in influenza A virus entry was explored. It has been found that the influenza A virus could trigger transient accumulation of autophagosomes at the early stage of infection and such induced autopahgosomes ferried incoming viruses deep into the cytoplasm for efficient infection. The incoming viruses were trapped into autophagosomes in a confined motional mode in the cell periphery and then underwent roughly a three-stage process towards the perinuclear region of the cell. Remarkably, this autophagic trafficking of viruses was independent of Rab5, a marker primarily associating with early endosomes. Overall, a dynamic and precise entry process of influenza A virus has been visualized and related mechanisms of distinct entry routes have been elucidated. Some new findings have further added significant knowledge about the virus entry.

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Preparation of nucleus targeting molecular capsule and its intracellular localization

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After the discovery of the unique property of Trans-Activator of Transcription (Tat) Protein of HIV-1 virus to translocate into cells, several peptides were reported to have the same property, and named as Cell Penetrating Peptides, CPP. One of the structural characteristics of CPP is the arginine rich sequences, where positive charge on guanidino group of arginine exist in dense. Due to the ability of CPP to translocate into cells, they are utilized as membrane permeability factor in many biological researches. It is also interesting that some CPP have a nucleus targeting ability.

Based on these reports, we have prepared a new molecular capsule with nucleus targeting property. In this research, we have used-cyclodextrin (-CD), a cyclic oligo saccharide composed of 8-D-glucopyranose units, as a molecular cage where molecules to be delivered from outside cell to the nucleus are loaded. All the primary hydroxy groups of -CD were substituted with guanidino groups to mimic the structural feature of arginine rich sequences of CPP. Fluorescein tag attached to the molecular capsule allowed us to observe the translocation of the capsule to nucleus of cultured fibroblast cells.

The transport efficiency of the capsule was evaluated by investigating the fluorescence of Rhodamine B, a fluorescent dye used as load molecule. A strong fluorescence of Rhodamine B was observed in cytoplasm and a weak one was observed in nucleus, indicating that the majority of Rhodamine B was transported to cytoplasm. Although the efficient translocation of the capsule to nucleus was observed, the efficiency of transport of the load molecule has room for improvement.

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Inhibitory effects of polymer encapsulated As_4S_4 on chronic myeloid leukemia cells through inducing cell cycle arrest and differentiation

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Realgar is a mineral drug widely applied in traditional Chinese medicine with the main component As_4S_4, which has been demonstrated to be effective in treating hematologic malignancies [1]. Nevertheless, the poor water solubility of As_4S_4 leads to the low bioavailability that has been an obstacle not overcome yet, though several groups have made various explorations. Aiming to increase the bioavailability of realgar and unravel the underlying mechanisms unknown, the raw As_4S_4 (r-As_4S_4) and an amphiphilic polymer were subjected to the hot melting coextrusion to fabricate a nano-formulation (e-As_4S_4), in which the crystal of r-As_4S_4 was crushed into nanoparticles that were encapsulated by the polymer simultaneously. In our previous work, e-As_4S_4 has been demonstrated the significantly higher treatment efficacy in the acute myeloid leukemia animal model in comparison with r-As_4S_4 [2].

This study focused on investigating the anti-cancer effect of e-As_4S_4 on K562 cells. In order to further increase the efficiency of r-As_4S_4 and reduce the dosage as well, the average particle size of e-As_4S_4 was decreased to 200 nm in reference to the 600 nm reported previously. We showed that the newly prepared e-As_4S_4 inhibited K562 cells growth significantly with the elimination of Bcr-Abl; the inhibitory efficiency was about 178 times more than that of r-As_4S_4.Meanwhile, e-As_4S_4 significantly increased the expression of CD235a and CD41, indicating that e-As_4S_4 induced both erythroid and megakaryocytic differentiation in the cells. Moreover, cell cycle arrest and apoptosis was clearly observed in the cells. The cell cycle was arrested in G2/M phase. In mechanistic studies, we found out that e-As_4S_4 increased p-perk and p-p38 MAPKs in K562 cells, which led to the cell cycle arrest and cell bi-direction differentiation respectively, possibly through modulating the level of cellular ROS. The results of this study therefore suggest that e-As_4S_4 represent an alternative therapeutic candidate for the treatment of CML.

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Peroxidase-like activity of apoferritin paired gold clusters for glucose detection

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The discovery and application of noble metal nanoclusters have received continuous attention. In this work, we found that apoferritin paird gold clusters (Au-Ft) system could efficiently catalyze oxidation of TMB by H_2O_2 to produce a blue color reaction. Compared with nature enzyme, Au-Ft exhibited higher activity near acidic pH and could be used over a wide range of temperature. Apoferritin nanocage could enhance the reaction activity of substrate 3,3,5,5-tetramethylbenzidine by H_2O_2. The reaction catalyzed by Au-Ft was found to follow a typical Michaelis–Menten kinetics. The kinetic parameters exhibited a lower K_m value (0.097 mM) and a higher K_{cat}value (5.8×10^4 s^{-1}) for TMB than that of HRP with strong robustness. Base on this finding, Au-Ft as peroxidas mimetics could perform an enzymatic spectrophotometric analysis of glucose. Au-Ft exhibited several advantages such as good stability, high catalytic efficiency, and excellent biocompatibility, which could be expected the more precise applications in future.

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Photothermal theranostic nanoprobes in the NIR-II window

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Optical transmission through tissue is optimal in the second near-infrared (NIR-II) window, which also allows higher maximum permissible exposure to laser irradiation relative to the commonly studied first near-infrared window. Thus, high efficiency photothermal agents suitable for this spectrum range are needed. Herein, I will discuss our research on the design and synthesis of self-doped semiconductor copper chalcogenides nanocrystals and their composites, as well as their application in photothermal therapy and active controlled drug release and imaging. First, by integrating noble metal nanoparticles with copper chalcogenides in one unit, synergistically enhanced NIR absorption is observed, due to the surface-enhanced EM field, making them highly promising NIR photothermal agents, as demonstrated by their in vivo photothermal performance in the NIR-II window with X-ray CT imaging capability. Furthermore, by coating the Au-$Cu_{2-x}S$ hybrids with mesoporous silica which can hold cancer drugs, a synergistic chemo-photothermal therapy can be achieved. Finally, tumor environment activated MRI imaging has been demonstrated using MnO_2 coated $Cu_{2-x}Se$ nano core-shell structures. These examples illustrate great potential of copper chalcogenide nanocrystals for photothermal theranostic applications in the NIR-II window.

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Applications of Raman spectrometry to cytological diagnosis

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Raman microspectroscopy is used in bio-medical studies including some cytological diagnoses. Conventional cytodiagnostic procedure is easy to perform and relatively non-invasive. Because the diagnosis can be more subjective and less accurate than histology, there are a certain number of “indeterminate” cases even though the number of collected cells is sufficient. Raman spectrometry to cytology as an adjunct to morphology is expected to improve the diagnostic sensitivity. However, no studies by Raman spectroscopy were reported forpleural effusion cytology. In this study, we measured Raman spectra of pleural effusion cells and tried to classify them into normal or cancer cells.

Raman measurements were performed employing a confocal micro-spectrometer equipped with 532 nm laser. Pleural effusion cells were collected from a lung cancer patient and a non-cancer patient. Cytological diagnoses were made by a cytotechnologist (IAC) and a board-certified pathologist. Obviously cancerous cells and mesothelial cells without staining were submitted for the measurements. RS data were analyzed by principal component analysis (PCA). The background spectrum was subtracted from the raw spectrum, and the intensity was normalized at 1086 cm^{-1}.

Though the spectra obtained from the benign and malignant cells did not seem to be visually different from each other, we could classify each cell into normal or cancer using PCA. The results suggest the Raman microspectroscopy might contribute to accurate cytological diagnosis of pleural effusions in clinical settings.

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DNA Hydrogels and their application in 3D Bioprinting

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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 kinds of pure or hybrid DNA supramolecular hydrogels, which could be formed under physiological condition within a minute at room temperature and without using any organic solvents. By tailoring the length of “sticky ends” of DNA linker, mechanical property of the hydrogel could be varied from hundreds to thousands Pa (G’, storage modulus); we also found that the viability of cell in a 4 mm diameter hydrogel is nearly 100% after 24 hours incubation from top in plastic tubes. These hydrogels possess extraordinary healing and fast-responding thixotropic properties, which make them injectable and writable. Because the formations of such hydrogels are based on DNA assembly, by DNA sequence design, they could be easily conferred excellent responsiveness including pH, DNA restriction enzymes, temperature etc., and enable easy removal after cell culture. In addition, we will show their application in 3D cell printing.

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Bioengineered surface design for mesenchymal stem cell culture

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Introduction: Mesenchymal stem cells (MSCs) are promising cell source for tissue regeneration. Much evidence has demonstrated that MSCs are capable of self-renewal and differentiate into multiple cell lineages. However, the number of MSCs that can be isolated from adult tissues is quite small, which limits the clinical application of MSCs for therapeutic purposes. Therefore, a novel culture protocol is absolutely required for the efficient expansion of MSCs. In MSCs culture, conventional polystyrene cell culture dishes are commonly used. However, it is not easy to maintain the proliferation potential and the stemness of MSCs on the substrates. On the other hand, basic fibroblast growth factor (bFGF) has been reported to be effective for the maintenance of MSCs. Therefore, we made attempts to immobilize bFGF onto the solid substrate for the expansion of MSCs.

Materials and Methods: bFGF carrying a hexahistidine (bFGF-His) was obtained from genetically modified E. coli. Then bFGF-His was immobilized onto the gold-coated glass surface introduced with Ni-NTA functional groups. The bFGF-His-immobilized substrates were exposed to citrate buffer solution for different durations to promote refolding of the bFGF-His on the surfaces. To examine the biological activity of the immobilized bFGF-His, MSCs were seeded onto the bFGF-His-immobilized surfaces and cultured for 6 days. Cells were observed every two days, and cell proliferation was analyzed on day 6. To investigate secondary structure of immobilized bFGF-His, 18 quartz plates ware used to immobilize bFGF-His and stacked together to obtain far-ultraviolet circular dichroism (CD) spectrum.

Results and Discussion: The rate of MSC proliferation was 1.6-fold higher on the bFGF-immobilized surface treated with citrate buffer, compared to the untreated surface. The CD spectrum of bFGF-His recorded just after surface immobilization indicated the presence of α-helix in the protein. Upon treatment with citrate buffer, negative Cotton effect specific for α-helix moderated with time of citrate buffer treatment, while that for β-sheet became noticeable. Because native bFGF is known to contain β-sheets but not α-helix, the results from solid-phase CD spectroscopy suggested that the bFGF domain in the engineered protein refolded into the native form-like structure in situ at the substrate surface. It is likely that this transformation activates the bFGF domain to promote MSC proliferation.

Our results showed that immobilized bFGF-His treated with citrate buffer was biologically active because its secondary structure approaches its natural state. This was well demonstrated by the cell culture experiments. It was concluded that substrates with immobilized bFGF-His served to enhance proliferation of MSCs after in situ treatment with citrate buffer.

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Nanotechnology for innovative cancer imaging and therapy strategies

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Nanomaterials especially functional inorganic nanomaterials exhibit a range of unique inherent physical and chemical properties useful in biomedicine. Starting from 2009, our research group has been working on the development of functional nanomaterials including sp2 carbon nanomaterials (carbon nanotubes and graphene), rare earth up-conversion nanoparticles (UCNPs), organic nanoparticles, and multifunctional composite nanostructures for applications in multimodal biomedical imaging, drug and gene delivery, as well as novel photo-therapies of cancer. In the meantime, we have also devoted considerable efforts to investigate the biological effects and toxicology of various nanomaterials at both cellular and animal levels. In this talk, I will focus on the development of natural biomaterials-based theranostics for in vivo multi-modal imaging-guided cancer treatment, as well as our recent efforts on the development of nanotechnology-based cancer immunotherapy.

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Dr. Zhuang Liu is a professor at Soochow University in China. He received his BS degree from Peking University (China) in 2004 and PhD degree from Stanford University (USA) in 2008. In 2009, He joined Institute Functional Nano & Soft Materials (FUNSOM) at Soochow University. His research interest is the development of functional nanomaterials for cancer theranostics. Dr. Liu has authored over 220 peer-reviewed papers, which have received a total citation of > 29,000 times and given him an H-index at 81. He was listed as one of the 'Highly Cited Researchers' by Thomson Reuters since 2015. He has been invited to be the Fellow of the Royal Society of Chemistry (FRSC) in 2015. He has received many academic awards, including the NSFC National Distinguished Scholar Fund, Biomaterials Science Lectureship, etc. Now he is serving as an associated editor for Biomaterials, and as editorial board members for a number of different international journals.

High efficient capture and isolation of circulating tumor cells on nano-bio interfaces

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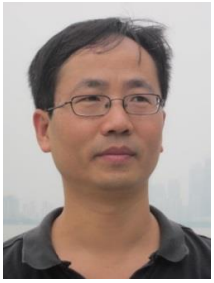
The high efficient capture and isolation of circulating tumor cells are considered to hold the key to enable potential early diagnosis, personalized therapy and therapeutic efficacy monitoring. To obtain the viable CTC samples is necessary for the subsequent molecular characterization and functional analysis, which is conceived to be of great significance for revealing the mechanism of tumor biology, cancer metastasis and drug sensitivity. It is still challenging to achieve the high efficient CTC isolation and viable CTC samples. In this presentation, we report high efficient capture and isolation of CTC based on nano-bio interfaces and interfacial aptamers and antifouling molecules. The chitosan nanofibers surface is firstly fabricated by electrospinning to provide a cellular compatible nano-interface, further modified by pCBMA as antifouling molecule and DNA aptamer as specific capture molecule, is capable of specific capture of viable rare CTC. Furthermore, a complementary sequence (CS) is used to efficiently hybridize with the aptamer to attenuate cell binding on interface, assisted by the flexible space provided by pCBMA brushes, and thereby the intact target cells could be nondestructively released from the substrate. Our work has potential to isolate the high pure and viable CTCs. Our work also shows how nanostructure and the interface moleculesregulate the morphology of the captured CTC, and reveals the importance of the controllable cell morphology on nano-bio interface for an effective nondestructive release of the captured CTC.

Renjun Pei



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Prof. Renjun Pei received his bachelor degree and PhD from Wuhan University, and is currently working at Suzhou Institute of Nano-Tech and Nano-Bionics, Chinese Academy of Sciences. He has been the recipient of the CAS Hundred Talents program. He is serving as editorial board member of Scientific Reports.

Research Interest:

Nano-based cancer diagnosis and translational research.

Aptamer SELEX and applications, for isolation of circulating tumor cells, MRI probes, targeted delivery platforms, 3D bioprinting etc.

TiO_2 nanoparticles-based nanomedicine for sonodynamic therapy

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A new modality of using ultrasound irradiation instead of photoactivation as in photodynamic therapy (PDT), sonodynamic therapy (SDT), has emerged as a promising treatment for various types of cancer. We focused on the ability of titanium dioxide (TiO_2) as sonosensitizer and TiO_2 has the ability to generate reactive oxygen species (ROS) by not only photo- but also ultrasound-irradiation. However, TiO_2 nanoparticles (NPs) have poor dispersion stability at physiological pH. To overcome this problem in SDT application, polyion complex (PIC) micelles were prepared by mixing TiO_2 NPs with polyallylamine bearing poly(ethylene glycol) grafts (PAA-g-PEG). Because the isoelectric point of the TiO2 NPs having a crystal structure of anatase is 6.2 and the TiO_2 NPs possess negative charges at neutral pH.
Here we would like to introduce two types of the therapeutic application of TiO2 NPs-incorporated PIC micelles. One is simple SDT, i.e. the evaluation of cell killing effect of PIC micelles by the sonication to the cells treated with the micelles, in which the generated ROS by sonication induce the oxidative damage to the cells. Another is the enhanced effect of siRNA gene silencing by sonication. PIC micelles could exhibit effective counter ion condensation effect to multivalent anions, and anionic siRNA was easily entrapped into PIC micelles. The siRNA-entrapped micelles were taken up into the cells. However, most of the micelles were located at endosome and lysosome. Under such situation, the sonication to the cells might induce the endosomal escape of siRNA through the ROS generation of TiO_2 NPs. And then, siRNA could exhibit its gene silencing effect. These results indicate that ROS generation ability of TiO_2 NPs by sonication could induce not only cell killing effect but also endosomal escape.

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Molecular engineering of polymers for cancer nanomedicine

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The cancer drug delivery process is a cascade of five steps consisting of Circulation in blood, Accumulation and Penetration in the tumor, cellular Internalization and intracellular drug Release, termed as a CAPIR cascade. The key to realizing high therapeutic efficiency of a nanomedicine is to maximize its each step efficiency, which is determined by the carrier's nanoproperties, i.e., Size, Surface and Stability properties (3S nanoproperties). Thus, the utmost challenge of cancer nanomedicine design is how to engineer the polymer carriers' functions into one system to gain all the needed 3S nanoproperties. Herein, we present our molecular designs of polymers to fabricate nanocarriers which can undergo "3S nanoproperty transitions" to make them adapt to the needs of each step and thereby achieve high therapeutic efficacy. One example is a nanomedicine likened to a "cluster bomb" capable of releasing small pH-sensitive drug-carrying nanoparticles (bomblets). This cluster bomb-like nanocarrier synchronizes pegylation-to-depegylation, large-to-small size, and neutral-to-positive charge, stable-to-instable (i.e. 3S nanoproperty) transitions, essential for accomplishing the CAPIR cascade. Another example is the charge-reversal polymers which can undergo stable-to unstable transition to facilitate DNA release and thus achieve highly effective and cancer-cells selective gene therapy. Finally, we will report the design of the first therapeutic dendrimer, which shows inherent and potent anticancer activity without any drug conjugation (Therapolymer).

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Strategies to enhance the siRNA delivery efficiency of non-virus carriers

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RNA interference (RNAi) is emerging as one of promising strategies for tumor therapy, especially for the treatment of leukemia. However, an efficient and safety non-virus delivery system for clinical siRNA therapy is still a major challenge. The most researched cationic non-viral vectors are limited because of their low transfection efficiency, especially in the serum containing mediums and real in vivo conditions. The difficulties of lysosome escape and nonspecific adsorption of serum proteins are considered the main barriers.

We prepared a cationized polysaccharide (Pullulan-spermine) and found that it is suitable for delivering siRNA into leukemia cells; To further improve the escape efficiency of siRNA from lysosomes and endosomes, we tried to introduce fullerene, a novel photosensitizer, to the reducing end of cationized dextran (C60-Dex-NH2). The result shows that visible light can trigger ROS generation, promote the escaping of carrier-siRNA complex from lysosome, and increase the interference efficiency both in vitro and in vivo; Finally, serum in the culture medium is one crucial factor that compromises RNAi efficiency of cationized non-viral gene carriers. However, the roles of serum in siRNA delivery process remain unclear. The mechanism of how serum affecting the siRNA delivery efficiency was studied. We found that N/P ratio is no more the most important factor in serum containing medium. Instead of traditional N/P ratio, S/C (Serum/ Cationic carrier) ratio is a more crucial factor during siRNA transfection process under serum containing conditions. Furthermore, when cationic carrer-siRNA complex were pre-coated by anionized polysaccharide, the adsorption of protein can be inhibited and the RNAi effect can be enhanced.

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Soft plasmonic nanomembrane as surface-attachable SERS substrates with high signal uniformity

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Building plasmonic assembiles enables new class of optical metamaterials, which are free-standing, one-particle-thick, supracrystalline structures constituted by metallic nanocrystals. Such novel plasmene nanosheets can generate enhanced electromagnetic fields via localized surface plasmon resonance and coupling effects between nanoparticles, which holds a great promise as an advanced suite for ultrasensitive detection of chemicals and food contaminants on real-world topologically complex surfaces.
Herein, we present a new class of SERS substrates – soft plasmonic nanosheets fabricated via polymer-based bottom-up self-assembly approach. Such nanosheets were ultrathin, mechanically flexible, optically translucent, enabling their attachment to real-world topologically complex surfaces for reproducible and sensitive detection of chemicals. The excitation wavelengths and SERS enhancement of nanosheets could be fine-tuned by adjusting sizes and shapes of constituent building blocks, as demonstrated by both experiment and simulation. Hence, excitation wavelength-specific SERS hotspots could be generated in a highly controlled manner. In addition, plasmonic nanosheets exhibited high structural homogeneity. This will enable their use as universal and unique SERS substrates with highly uniform Raman hotspot distributions across large areas for rapid and sensitive multi-phase detection of chemical species in multiphase, and even on topologically complex solid surfaces. Also, we will discuss the possible application trends for those plasmonic nanoarchitectures, and present our perspectives on the opportunities and challenges in this emerging field.

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