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Fluorescence microscopy has become a powerful tool for real time visualizing, monitoring and tracking molecules and their dynamic changes in material science and biological application, due to its high selectivity, remarkable sensitivity, excellent spatial and temporal resolution and non-invasive operation. It is long believed that the development of highly efficient fluorophores relies largely on the high electronic conjugation. However, such traditional fluorophores are prone to aggregate with light emission quenching which is known as aggregation-caused quenching (ACQ). On the other hand, these exogenous dyes used for bioanalysis and bioimaging probably showed high tototoxicity to living samples.

We have observed an opposite phenomenon termed “aggregation-induced emission” (AIE) and many AIE luminogens (AIEgens) based on conjugated systems have been developed and applied in chemosensing, bioprobe, bioimaging, diagnosis and therapy and other applications.[1] In addition, we have developed several non-conjugated systems, such as poly(maleic anhydride), polypeptides, amino acid and tetraphenylethane, which show low or none emission in solution state but bright and long-wavelength emission in solid state. We termed this kind of fluorescent materials as “clusteroluminogens”. [2-3] Giving their formation of nanoaggregate in solid state, these special AIEgens could also be termed as “nanocluster”. Further experiments and theoretical calculation suggest the through-space conjugation plays an important role in the luminescence. Meanwhile, hydrophobic effect and dipolar interaction serve as the influential force to facilitate the formation of cluster within the process of aggregation. This kind of luminescent nanoclusters only consists of small phenyl ring and other functional group like carboxyl, amide, ester, et al., rendering them as extraordinary biocompatible bioprobes for bioimaging and biodetection in living samples. In addition, the inter- or intramolecular interaction changes of these nanoclusters can be adjusted by mechanical force, which could potencilly made them useful in detecting mechanical force in material science and living systems.[4]

Keywords: AIEgen, nanocluster, luminescence, biocompatibility, imaging

Reference
In Vivo Production of Designed RNA Nanostructures

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Programmed self-assembly of nucleic acids is a powerful approach for nanoconstructions and the assembled nanostructures have been explored for various applications in nanoplasmics, molecular computations, drug delivery, bioanalytics, biophysics, etc. The nucleic acid assembly often requires chemical or in vitro enzymatical synthesis of DNA or RNA. It is not a cost-effective production method at large-scale. In addition, the difficulty of cellular delivery of nucleic acids limits the in vivo applications of nucleic acid nanostructures. To solve those problems, herein we report a strategy that mimics protein production. RNA gene-encoding DNA duplexes are transcribed into single-stranded RNAs (ssRNAs), which self-fold into well-defined RNA nanostructures in the same way as polypeptide chains fold into specific 3D structures, proteins. The resulting RNA nanostructure contains only one component RNA molecule. This approach allows both in vitro and in vivo production of RNA nanostructures. In vivo synthesized RNA strands can fold into designed nanostructures inside of cells. This work not only suggests a way to synthesize RNA nanostructures at a large-scale and a low cost but would also facilitate the in vivo applications of RNA nanostructures.

![Scheme of in vivo production of an RNA structure that has a shape of “8”](image)

Fig. 1 Scheme of in vivo production of an RNA structure that has a shape of “8”.

Keywords: RNA Nanostructures, RNA Nanotechnology, Self-Assembly, In Vivo, Folding.

Reference
Nanozyme Integrated Point of Care Biosensors for E-health

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In recent years, much effort has been devoted toward developing point-of-care (POC) devices. Among them, smart phone enabled paper-based POC devices are a special category due to the advantages of being simple, rapid, on-site, and cost-effective; they have been widely used in home health care and medical testing, even environmental monitoring. The blood glucose meter is one of the most successfully commercialized diagnostic devices on the market because of its low cost, compact size, simple operation, and reliable quantitative results. However, the glucose meters are generally used for only glucose testings. Recently, many groups have reported methods establishing a direct relationship between the concentrations of the targets in the samples and the glucose detected by a glucometer, enabling a number of non-glucose biomarkers to be detected quantitatively.

In this talk, we describe a novel design that combines the traditional lateral flow strip with a commercialized smartphone-enabled glucometer for portable and quantitative detection of a non-glucose target. The concept is demonstrated by using an oxidative DNA damage biomarker, 8-hydroxy-2’-deoxyguanosine (8-OHdG)¹ ². The basic design of the device a colorimetric visual detection platform based on the integration of nanozyme and immunoassay. The visual detection can provide only qualitative and semiquantitative results. Thus, to enable quantitative analysis, we establish a novel method that transforms the detection of the target to the detection of an nanozyme based converting enzymatic reaction. Considering the inherent advantages of the personal glucose meter, the demonstration of this device, therefore, should provide new opportunities for the monitoring of a wide range of biomarkers and various target analytes in connection with different molecular recognition events.

Acknowledgement: This work was supported by NSFC NSFC 21729501 project and the Engineering Research Centers Program of the National Science Foundation under NSF Cooperative Agreement No. EEC-1648451.

Keywords: nanozyme, smartphone, POCTs, LFA

Reference
Framework nucleic acids-guided molecular sensing and imaging

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Proteins and nucleic acids are dynamically organized in cells to realize their physiological functions with spatial and temporal orderliness. This type of elegant supermolecular assembly has inspired researchers to create molecular/biomolecular structures with dynamic organization outside of the cells. In particular, DNA nanotechnology has proven to possess extraordinary flexibility and convenience for “bottom-up” construction of exquisite nanostructures with high controllability and precision, which holds great promise in a wide range of applications, e.g., nanofabrication and molecular electronics, in-vivo and in-vitro sensing and drug delivery.

In this talk, I will present several examples of using framework nucleic acids (FNAs) for dynamic organization of biomolecules in vitro and in vivo. FNAs are DNA architecture with high structural stability and designable mechanical rigidity, which are suitable for organization of higher-ordered nanocomplexes and nanodevices. As examples, we employed FNAs to engineer the biosensing interface and cytoplasmic interface for molecular diagnosis and imaging.

Keywords: framework nucleic acids, biosensor, supermolecular assembly

References

New tools for liquid biopsy:
rare cells, exosomes, and circulating DNA

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This presentation will describe new technologies we developed for liquid biopsy and precision medicine. The three new tools include a rare-cell isolation instrument we call eDAR (ensemble decision aliquot ranking), a nanofluidic technology for the high-sensitivity sorting of exosomes, and a digital-nucleic-acid detection and analysis platform based on our SD (self digitization) chip. I will outline the workings of these new tools, describe their performance, and discuss the clinical questions we are addressing with these next-generation technologies.

**Keywords:** Rare Cells, CTCs, Exosomes, Cell-Free DNA, Circulating DNA
Aptamers for the imaging of subcellular structures

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Aptamers are synthetic single-stranded oligonucleotides (DNA or RNA) with high selectivity and specificity toward various targets, and have shown great promise in target therapeutics, diagnostics, and biomedical analysis.1-3 Aptamers are generated by an iterative in vitro target binding and enrichment process known as SELEX (Systematic Evolution of Ligands by EXponential enrichment)1. The targets of aptamers range from small molecules, proteins to cells and tissues. Compared to aptamer selection against purified targets that only get aptamers recognizing the pure molecules, selection using complex targets (such as cells, bacteria and tissues) is able to generate aptamers that recognize prior unknown molecular signatures on these targets.4-5 Since molecular signatures on specific cells are far from been understood, aptamer selection against complex targets provides the opportunity to the discovery of new molecular events.6 Here, we report two aptamers, M17A2 and yly12, that were selected against doxorubicin-resistant breast cancer cell line (MCF-7R) and the neurites between differentiated SH-SY5Y cells respectively. Aptamer M17A2 specifically binds a kind of intercellular connections that can transport drug resistance-related proteins between cells. Aptamer yly12 specifically binds neuronal cell adhesion molecule and can image the 3D neurite network between neural cells.

Fig. 1 Aptameric probe images intercellular connection (left) and 3D neurite network (right)

Keywords: Aptamers, SELEX, Intercellular connection, Neurite

References
Using Microwell Array Technology to Probe Chemistry and Biology at Their Fundamental Limits

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Abstract
We use microwell arrays to detect and study single molecules. Our group has developed a single molecule detection technology, called Simoa for single molecule arrays, to detect proteins at 1000 times lower concentrations than conventional methods, thereby opening up an entirely new set of proteins that can now be detected in the blood. The technology is being used in clinical studies to develop a blood test for detecting early-stage breast cancer, for diagnosing latent tuberculosis, and for detecting various infectious diseases using the host response to infection. We have also developed methods to measure the concentrations of key biomolecules in single cells. The research has important implications for understanding the stochastic nature of biological systems as well as for practical applications in which cells are used to assess toxicity and bioavailability. In addition, the laboratory is using arrays of single molecules for fundamental enzymology studies.

Fig. 1 Antibody beads in microwells provide single molecule detection

Keywords: keyword 1, Single molecule 2, proteins 3 microwells

Reference
Quantum dynamics studies of chemical reactions involving methane

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Reactions occurring at a carbon center are one of the most important and useful classes of reactions in chemistry. The simplest type at a carbon atom with a tetrahedral environment is that of an atom reacting with methane, in which the incoming atom can either abstract or substitute a hydrogen atom in methane. Theoretically, this type of reactions can be studied reliably only by using quantum dynamical method because of at least four hydrogen atoms involved. However, it is very challenging to study this kind of reactions quantum mechanically due to the fact the computation efforts increases exponentially with the number of atoms involved in a reaction. In this talk, I will present some of our recent quantum dynamics results for the H+CH₄ substitution reaction and the Cl/F+CH₄ abstraction reactions. It will be shown that our calculations can not only provide physical insights into some interesting experimental observations on these reactions, but also provide some clues to the failure of experiment.

Keywords: chemical reaction dynamics, quantum dynamics, isotope effect, heavy-light-heavy oscillations, vibrational excitation effect
The Frame Guided Assembly

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How to precisely control the shape and size of final assemblies, especially using same amphiphilic molecules and under the same environmental conditions, is always a challenge in molecular assembly. Inspired by the cytoskeletal/membrane protein/lipid bilayer system that determines the shape of eukaryotic cells, we proposed and ‘the Frame Guided Assembly’ (FGA) strategy to prepare heterovesicles with programmed geometry and dimensions. This method offers greater control over self-assembly: with same molecular system, the size of final assemblies could be tuned at 1 nm level and their shape could vary from spherical to cubic, and even given sized two dimensional sheets. Most importantly, the principle of the FGA could be applied to various materials such as block copolymers, small molecules including surfactants and lipids, which is a general rule in self-assembly.

Scheme 1. Schematic illustration of the Frame Guided Assembly

References


Biography

Dongsheng Liu learned polymer sciences in University of Science and Technology of China and graduated with a B.S. degree in 1993. He then worked as a research associate in the Institute of Chemistry, CAS for six years and earned his Master degree on polymer chemistry in 1999. From 1999 to 2002, he finished his Ph.D study on the self-templated DNA circularization in the Hong Kong Polytechnic University under the supervision of Professor Albert S. C. Chan. In 2003, he joined the Chemistry Department of Cambridge University as a postdoc research associate, worked on DNA nanotechnology with Professor Shankar Balasubramanian. In 2005, he joined the National Centre for NanoScience and Technology, China as a principle investigator and in June 2009, he moved to the Department of Chemistry, Tsinghua University as a full professor. He was awarded the 1st “CCS-RSC Young Chemist Award” in 2008, the 7th CCS-BASF Youth Innovation Prize in 2014. Dongsheng was invited as FRSC in 2011 and became “Changjiang” Chair Professor in 2015. His research mainly focuses on DNA molecular machines and DNA based smart materials.
Second Step towards Optical Force Chromatography: Molecule Disperser

Using a Standing Wave

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In molecule optics, a matter wave of molecules is manipulated by a molecule-optical component made of external, typically radiative, fields. The molecule-optical index of refraction, n, for a nonresonant IR laser pulse focused onto a molecular beam can be obtained from the energy conservation and wave properties of molecules. Since n depends on the properties of molecules as well as those of the laser field, a multi-component molecular beam can be separated into components according to their molecule-optical refractive indices n by optical force chromatography. We obtained a chromatographic resolution of 0.90 for the spatial separation of a mixture beam of benzene and nitric oxide using a focused Nd:YAG laser pulse. As a next step, we report a molecule disperser using a standing wave. The steep gradient of the standing wave potential imparts far stronger dipole forces on the molecules than propagating pulses do. Moreover, large changes in the transverse velocities (i.e., up to 80 m/s) of CS\textsubscript{2} molecules in a molecular beam obtained with the standing waves were well reproduced in numerical simulations using the effective polarizability that depends on the molecular rotational states.

![Fig. 1](image_url)

**Fig. 1** The velocity map ion images of CS\textsubscript{2} molecules (a) without any IR laser, (b) with IR of \(I_0 = 4.9 \times 10^{10}\) W/cm\(^2\), and (c) with the pulsed optical standing wave made of two IRs of \(I_0 = 4.9 \times 10^{10}\) W/cm\(^2\). The color bar in the image denotes the fraction of the molecules.

**Keywords:** Molecule optics, optical force chromatography, standing wave
A Study of Nanozymes
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Over the past few decades, scientists established artificial enzymes as alternatives to natural enzymes in a wide range of applications. Why artificial enzymes? Mainly because of the high stability and low cost of the artificial enzymes as compared to those of natural enzymes, although they have many unique merits. A variety of materials have been extensively explored, among which the nanomaterials with enzymatic characteristics, named “nanozymes” are most exciting. New system of peroxidase mimetics based on nanomaterials has been initiated and developed firstly with iron oxide (Fe₃O₄ MNPs) which can imitate peroxidase catalytic activity by X Yan group published in Nat. Nanotechnol., 2007, 2, 577-583 and then reviewed by H Wei and E Wang in Chem.Soc.Rev.2013,42, 6060-6093, “Nanozyme:Next-generation artificial enzyme”. Since then the nanozymes have developed very rapidly in China as well as in the world. In this talk we will deal with the carbon based nanomaterials, metal based nanomaterials, metal oxide based nanomaterials, metal alloy based nanomaterials and metal organic frame based nanomaterials.

We have explored novel peroxidase mimetics based on nanomaterials like TiO₂ NTA; PdPt NWs and PdPt NSs; NiPd hNPs; PRGI/Pt(surface charge-controlled assembly) and tandem catalysis. We have also enhanced functions of the peroxidase mimetics to widen applications like glucose assays; controlling biocatalytic activity; SNPs determination and bioactive paper for diagnostics.

Keywords: Nanozyme, Artificial enzyme; Iron oxide Fe₃O₄ MNPs; TiO₂ NTA; PdPt NWs; PdPt NSs; NiPd hNPs; Tadem catalysis

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Detection of Biomolecules Based on Nanopores

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Nanopores with functional elements (FE) have shown promise for rapid DNA sequencing, sensitive single-molecule sensing and specific ion gating\textsuperscript{1, 2}. Ionic current measurement is currently a benchmark but focused solely on the contribution from nanopores inner wall FE (NIWFE)\textsuperscript{3}; the attributes of FE at nanopores outer surface (NOSFE) is nearly ignored yet remains exclusive. Here, we show that the role of NOSFE and NIWFE for ion gating can be distinguished by incorporating electrolytic current and ionic current signals through formation of exquisite DNA architectures acting as both molecular switch and ion gate, which behave continuously tunable and reversible ion gating ability. We find that NOSFE itself exhibits negligible ion gating behavior, but it can produce synchronously enhanced effect when alliance with NIWFE. Moreover, the high-efficiency gating systems display more noticeable synchronous effect than the low-efficiency ones. We also reveal that the probe amount of NOSFE and NIWFE is almost equally distributed in our biomimetic nanopores, which is potentially a premise for the synchronously enhanced ion gating phenomena. The uncovered ion gating function of NOSFE might be extended to nanopore-based DNA sequencing and single-molecule sensing.

**Fig. 1** (a) Graphical illustration of nanopores functional regions (NIW, NOS, NIW + NOS) associated with ion gating efficiency to be investigated. (b) Cartoon presentation of DNA based functional elements (FE) regionally assembled at different regions of AAO-Au nanopores. Shown inset was a DNA traditional sandwich (TS) tethered with double MB electrochemical tags. CP, capture probe; SP, signal probe.

**Keywords:** Nanopores, Functional elements, Ion transport, Outer surface

Reference

NIR Nanoprobes for Multiplexed Biodetection

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The identification of potential diagnostic markers and target molecules among the plethora of tumor oncoproteins for cancer diagnosis requires facile technology that is capable of quantitatively analyzing multiple biomarkers in tumor cells and tissues. Diagnostic and prognostic classifications of human tumors are currently based on western blotting and single-color immunohistochemical methods that are not suitable for multiplexed detection. Herein, we report a general and novel method to prepare single-band upconversion nanoparticles with different colors. The expression levels of three biomarkers in breast cancer cells were determined using single-band upconversion nanoparticles, western blotting and immunohistochemical technologies with excellent correlation. Significantly, the application of antibody-conjugated single-band upconversion nanoparticle molecular profiling technology can achieve the multiplexed simultaneous in situ biodetection of biomarkers in breast cancer cells and tissue specimens and produce more accurate results for the simultaneous quantification of proteins present at low levels compared with classical immunohistochemical technology.

Keywords: Rare Earth Luminescent Nanomaterials, Near-Infrared, Biomedical Analysis

Fig. 1 Microcarrier fate tracking and drug-release monitoring by the ACIE bioimaging system using an InGaAs CCD camera. After oral administration, the BSA–NPTAT-loaded microcarriers showed little protein drugs leakage in the GI tract (pH¼41) but sustained release in the intestine (pH¼8) due to the deprotonation of the SSPI on the outer surface of the microcarrier.

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Reference
Engineered nanomaterials and new analytical methods for biomedical applications

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Rapid advancements of engineered nanomaterials offer great opportunities for biomedical applications. We will present our recent results on the detection of molecular biomarkers and nanomaterials for biotherapy. Using engineered nanomaterials, along with new analytical methods such as surface plasmon resonance and immunoassays, we have carried out sensitive detections of various biomarkers ranging from Alzheimer’s disease biomarkers (e.g. Aβ (1–40), Aβ (1–42)) in cerebrospinal fluid to cancer biomarkers (e.g. microRNAs) in serum. We have also studied the interaction between different biomarkers (e.g. amyloid beta peptides, Tau, TTR, and metal ions) to reveal the pathogeny of Alzheimer’s disease. We will also present some recent results related to cancer therapy.

Keywords: nanomaterials, biomarker detection, cancer therapy
Employing the property that self-assembly of probes can enhance imaging signals, we have conducted sensitive analyses on several important biomarker-instructed self-assembly processes. 1) By rational design of a system of one enzyme (alkaline phosphatase) two substrates, for the first time, we have successfully used chemiluminescence imaging to precisely analyze the simultaneous enzyme-instructed self-assembly process. 2) Using cryo transmission electron microscopy imaging analysis, we have differentiated several nanofibers which were obtained from different biomolecule-instructed self-assemblies at angstrom scale. 3) By designing small molecular probe (or drug), we have conducted real time fluorescence imaging (or magnetic resonance imaging, etc) analyses on the intracellular enzyme-instructed self-assembling processes of nanoprobe (or drugs).

References

Author Biography
Prof. Gaolin Liang received his B.S. from Nanjing University in 1993, M.S. from Zhengzhou University in 2002, and Ph.D. from Fudan University in 2005. From 2005 to 2008, he was a postdoctoral fellow at The Hong Kong University of Science and Technology under the supervision of Prof. Bing Xu. From 2008 to 2010, he was a postdoctoral fellow at Stanford University under the supervision of Prof. Jianghong Rao. Prof. Liang’s research interests mainly focus on nanochemistry, molecular and cellular imaging, and biomedical analysis.
Tumor microenvironment targeting nanorobots: a promise for a cure of cancer?

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Tumor microenvironment plays critical roles in tumor growth, malignant transformation and metastasis. Precise design of intelligent nanomedicines for regulation of tumor microenvironment offers a great promise as a feasible and fruitful strategy to improve the therapeutic outcomes for cancer treatment. Our recent development on peptide-, protein- and DNA-based biomedical nanorobots or nanomachines has been made to regulate tumor microenvironment, to block tumor microvessels or re-store the homeostasis of tumor stroma. Given the robust functionality, exceptional designability, potent antitumor activity and minimal in vivo adversity, the nanorobots represent the next generation of nanomedicine and a promising strategy for precise drug design for cancer therapeutics.

References
**Author Biography**

Guangjun Nie is a Professor at the National Center for Nanoscience and Technology, China. He obtained his Ph.D degree from Institute of Biophysics, Chinese Academy of Sciences in 2002. From 2002 to 2008, he worked as postdoc fellow at Jewish General Hospital, McGill University, Canada. He was awarded the National Distinguished Youth Scientist in 2013 and the Hundred Talent Program Scholar of CAS in 2008. He was a Chief Scientist of a MoST National Basic Research Program (2012-2016), and then is the Chief Scientist of a MoST National Basic Research Program (2018-2022). He has a long standing interest in cancer biology, blood physiology and pathophysiology of human disorders. Currently, his main interests are design of bio-inspired materials to overcome the current barriers in tumor therapy and nanomedicines. In particular, his group is working toward controlling the chemical properties of multi-functional nanoparticles in order to allow specific targeting and regulation of tumor cells and their microenvironment.

His research interests include: 1) Targeting and regulation of tumors and their microenvironment mediated by intelligent functional nanomaterials for diagnostic and therapeutic applications, especially pancreatic and liver cancers. 2) Novel biomaterials design and synthesis inspired by biological systems and design of functional molecular machinery. 3) Cellular membrane vesicle systems and the roles of exosomes in biological effects of nanomaterials and drug delivery. 4) Development of novel nanomedicines for treatment of major human diseases, such as metabolic diseases, neurodegenerative diseases and iron and redox related human disorders.

His most recent research activities generated a group of interdisciplinary works in nanobiology, nanomedicine and blood physiology fields, including over 130 papers published in Nature Biotechnology, Nature Biomedical Engineering, Adv Mater, Angew Chem, JACS, Nano Letters, Blood, Biomaterials, Br J Haematol, JBC, Cancer Letters, Molecular Cancer Therapeutics. He has filled over 40 patents on novel nanomedicines and 22 of them have been granted, with two patents transferred to the biotechnology industry. He is an experienced supervisor of postgraduate students and collaborates widely both within China and internationally. He is also the Affiliated Professor of Northeast Normal University, Changchun and East China University of Science and Technology, Shanghai. He is also an Affiliated Senior Member of Houston Methodist Research Institute, Houston, US.
Lymph-node-targeting neoantigen nanovaccine for combination cancer immunotherapy

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The immune system in cancer patients is systemically suppressed, and cancer immunotherapy aims to normalize the immune system to harness the power of immune system to systemically treat cancer. The past decade has witnessed the breakthrough of cancer immunotherapy, including immune checkpoint inhibitors, chimeric antigen receptor T cells, and cancer vaccines. Despite tremendous potential of molecular subunit vaccine for tumor immunotherapy, its clinic outcome has been suboptimal, largely due to inefficient co-delivery of heterogeneous peptide antigens and adjuvants to secondary lymphoid tissues such as lymph nodes (LNs). Here, by conjugating albumin-binding Evans blue (EB) with vaccines, we developed albumin-binding vaccine (AlbiVax) that, via in vivo assembly of albumin/vaccine nanocomplexes, were co-delivered to LNs more efficiently (20-fold for CpG, 91-fold for antigen) than unconjugated vaccine or vaccine emulsified in Incomplete Freud’s Adjuvant (IFA), a benchmark adjuvant in clinical trials. Multi-scale pharmacoimaging was employed to study AlbiVax: by PET imaging in small animals, we systematically optimized AlbiVax for LN delivery; by light-sheet fluorescence imaging, we elucidated the distribution of AlbiVax in draining LNs that were cleared to be transparent; and by super-resolution imaging, we discovered efficient intracellular co-delivery of AlbiVax via albumin into endolysosome of antigen-presenting cells. AlbiVax elicited 21-fold higher frequency of Antigen-specific CD8+ cytotoxic T lymphocytes than IFA-emulsified vaccine, and induced immune memory for > 5 months, making AlbiVax a potent T cell vaccine for cancer immunotherapy. AlbiVax dramatically regressed or inhibited the progression of established primary or lung metastatic tumors. Remarkably, combining AlbiVax with immune checkpoint inhibitor anti-PD-1 further improved the therapeutic efficacy and increased the complete regression rate for the therapy of MC38 tumor. Together, AlbiVax represents a widely applicable and robust T cell vaccine for cancer immunotherapy.

Keywords: nanovaccine, subunit vaccine, albumin, pharmacoimaging, combination cancer immunotherapy

Reference
In vivo self assembled biomaterials for bioimaging and therapeutics

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Traditional strategy for specific drug delivering is by constructing a responsive nanocarrier, which prove to effective in increasing drug efficiency and decreasing side effects. Various research can improve delivery efficiency by introducing active targeting, passive targeting and long-term circulation motif to molecular design. Whereas, impute efforts do not correlate with clinical transform.

Researchers are enlightened by self-assembly process in nature, which is happening all the time and all the where, and plays both positive and negative roles in the body. Self-assembly tells that many components will aggregate into specific pattern or structure without other intervening forces. Herein, our strategy is going to construct in vivo self-assembly, by instructing molecules to self-assembly into highly-ordered structures under specific biological and pathological sites in terms of cells, tissues and even animals. These assemblies show higher accumulation and longer retention in-situ. Therefore, it is promising to achieve enhanced theranostic effect. Enzyme is a widely spread and specific catalyst, it is promising to manipulate enzyme triggered peptide self-assembly in specific disease site.

Peptide self-assembly have been widely researched. Phenylalanine and diphenylalanine are reported minimum self-assembled amino acid and dipeptides. Some self-assembled short peptides and their derivative are rich in aromatic group, e.g., Fmoc-Phe-Arg, Cys- Phe- Phe. Some phosphorylated short peptides are hydrophilic, which would turn into hydrophobic and then self-assemble into hydrogel after phosphatase cleavaging phosphate group. Peptide amphiphiles can self-assembled into multi-morphologies and have showed widespread application in regenerative medicine, which also showed enzymatic-controllable self-assembly. Polypeptides, peptide-polymer complexes and nature-derived peptides are also applicable for constructing self-assemble system. Some enzymes are overexpressed in disease site, so we can design enzyme triggered self-assembly, therefore increasing imaging sensitivity and efficiency of chemotherapy, and also showed decreased toxicity duo to biocompatible peptides used. In a word, in vivo self-assembly is of great potential to explore its application in disease theranostics.

Keywords: In vivo self assembly, bioimaging, drug delivery

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Photo-switchable & responsive compounds are core organic molecules which can undergo reversible photochemical reactions between two chemical species with distinct properties. Introducing these photo-switchable & responsive core units into supramolecular self-assembling systems endows the supramolecular nanostructures or materials with intriguing responsive behavior to light, which can be conveniently orthogonal to other stimuli. From another perspective, the well-ordered supramolecular structures or materials with complexity and stimuli-responsive properties have the capability to “amplify” the light-controlled conformation changes, thus producing more sophisticated functions. This lecture mainly highlights the recent advances achieved in our laboratory in fabricating artificial supramolecular self-assembling systems with photochromic compounds as light-responsive units. Most recently, an innovative strategy was presented in our labs to construct amorphous metal-free RTP small molecular compounds.
Bioimaging for In situ Sensing of Cellular Functional Molecules

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Cellular functional biomolecules have been regarded as attractive targets for biomedical research, molecular diagnostics and disease therapy. Our recent efforts have been devoted to in situ analysis and highly selective detection of various cellular functional biomolecules, and in situ visualization of intracellular glycosylation and curative effect during precise near-infrared or gene cancer therapy. Here I will introduce our research results in design of bioimaging and signal amplification strategies for in situ sensing of cellular functional biomolecules, including electrochemical, scanometric, chemiluminescent, fluorescence, and Raman spectroscopic techniques. These sensing methods have been used for detection and in situ analysis of glycans [1], protein-specific glycans [2] and gangliosides [3] on living cell surface, intracellular microRNA [4], sialyltransferase, lysosomal neuraminidase and glycosylation [5], telomerase [6], ATP and caspases [7]. Some bioimaging strategies have been used for real-time monitoring of cell–subtype specific siRNA delivery [8], and precise therapy against cancer [7,9].

Keywords: bioimaging, in situ sensing, cellular functional molecules

Selected references:
Selective Capture of Bioorganic Phosphates on TiO$_2$ Nanowire Arrays from Biofluids for Molecular Characterization by Internal Extractive Electrospray Ionization Mass Spectrometry

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Bioorganic phosphates are ubiquitous in biofluids and associated with various pathophysiology processes\cite{1}. Rapid quantitative detection of trace bioorganic phosphates in biosamples is of sustainable interests in multidiscipline of life science. Herein a novel analytical strategy based on internal extractive electrospray ionization mass spectrometry\cite{2, 3} is proposed (Fig. 1), for which homemade TiO$_2$ nanowire arrays were constructed to selectively capture bioorganic phosphates including phospholipids, phosphopeptides, phosphocreatine, glucose-6-phosphate, uridine 5'-monophosphate, etc, in biofluids when the complex biosample adjusted to low pH values (pH=2-3) with 1% TFA (v/v) was loaded to the array of TiO$_2$ nanowires. After enrichment, the phosphates were released by a charged extracting solvent (1.5% ammonia methanol, w/w), which was nebulized in front of the ion entrance of the mass spectrometer to generate the analyte ions for mass analysis. The complexed matrices imposed no serious interferences on the qualitative and quantitative analysis of phosphates in either human plasma, whole blood, undiluted human urine, or protein digest. Based on the phospholipids levels in plasma, ovarian cancer was confidently visualized by processing the mass spectral data using partial least squares discriminant analysis (PLS-DA). A single sample analysis was accomplished within 2 min. The results demonstrated that the TiO$_2$ nanowire arrays iEESI-MS servers a platform for trace detection of bioorganic phosphates in various biofluids, with merits such as high sensitivity, high accuracy, low sample consumption, and high throughput.

![Fig. 1. Schematic illustration of TiO$_2$ nanowire arrays iEESI-MS.](image)

**Keywords:** Mass spectrometry, TiO$_2$ nanowire arrays, Extractive electrospray ionization, Bioorganic phosphates

**Reference**

Synthesis of Novel Two-Dimensional Nanomaterials for Sensing Applications

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Abstract
In this talk, I will summarize the recent research on synthesis, characterization and applications of two-dimensional (2D) nanomaterials in my group. I will introduce the synthesis and characterization of novel two-dimensional nanomaterials, such as graphene-based composites, single- or few-layer metal dichalcogenide nanosheets and hybrid nanomaterials, 2D metal-organic frameworks (MOFs), 2D covalent organic frameworks (COFs), etc. Then I will demonstrate their applications in chemical and bio-sensors.

Keywords: Two-dimensional nanomaterials; Graphene; Metal dichalcogenides; Nanodevices; Field-effect transistors; Sensors

Brief CV
Dr. Hua Zhang obtained his B.S. and M.S. degrees at Nanjing University in China in 1992 and 1995, respectively, and completed his Ph.D. with Prof. Zhongfan Liu at Peking University in China in July 1998. He joined Prof. Frans De Schryver’s group at Katholieke Universiteit Leuven (KULeuven) in Belgium as a Research Associate in January 1999. Then he moved to Prof. Chad A. Mirkin’s group at Northwestern University as a Postdoctoral Fellow in July 2001. He started to work at NanoInk Inc. (USA) as a Research Scientist/Chemist in August 2003. After that, he worked as a Senior Research Scientist at Institute of Bioengineering and Nanotechnology in Singapore from November 2005 to July 2006. Then he joined the School of Materials Science and Engineering in Nanyang Technological University (NTU) as an Assistant Professor. He was promoted to a tenured Associate Professor on March 1, 2011, and Full Professor on Sept. 1, 2013.


Dr. Zhang's research is highly interdisciplinary. His current research interests focus on the crystal phase engineering of nanomaterials and controlled epitaxial growth of heterostructures, including the synthesis of ultrathin two-dimensional nanomaterials (e.g. metal nanosheets, graphene, metal dichalcogenides, metal-organic frameworks, covalent organic frameworks, etc.), novel metallic and semiconducting nanomaterials and their hybrid composites, for applications in catalysis, clean energy, (opto-)electronic devices, nano- and biosensors, water remediation, etc.
Spectroscopic Probes and Sensing Analyses (2018)

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Spectroscopic probes have been widely studied and used in many fields due to their powerful ability to increase analytical sensitivity, and especially to offer superior temporal and spatial sampling capability for imaging analysis. Our research group has been engaged in this area for two decades, during which a series of new spectroscopic probes for biological substances have been developed by using suitable chemical reactions [1]. In this talk, special focus will be on our recent researches on the new spectroscopic probes and sensing analyses for some enzymes such as tyrosinase, monoamine oxidase A, and nitroreductase [2-5].

Keywords: spectroscopic probes, sensing analysis

References

What else can you see with X-rays?

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This talk describes passive chemical and mechanical sensors that are read using X-ray projection imaging (plain radiography). X-rays are beautifully-suited for imaging anatomy and associated pathologies because they penetrate through deep tissue and show contrast between air, soft tissue, bone, and metal hardware. Consequently, physicians routinely employ radiography during diagnosis, surgical intervention, and patient follow-up. However, X-rays are usually blind to local biochemical information (e.g., pH) and insensitive to small biomechanical changes (e.g., in mechanical strain and pressure). Such information is critical for studying, detecting, and monitoring pathologies associated with implanted medical hardware, such as fracture non-union and implant-associated infection. We address this limitation by attaching to the medical implant surface a transducer that converts the chemical or mechanical signal into motion of a radiopaque dial or fluid. For example, a polyacrylic acid-based hydrogel with pH-dependent swelling was placed on an orthopedic plate. The pH could then be determined by from the extent of hydrogel swelling by measuring the position of a radiopaque indicator pin embedded in the hydrogel. The pH sensor was calibrated in a series of standard pH buffers and tested during bacterial growth in culture. Its response was negligibly affected by changes in temperature and ionic strength within the normal physiological range. Radiographic measurements were also performed in cadaveric tissue with the sensor attached to an implanted orthopedic plate fixed to a tibia. Pin position readings varied by 100 µm between observers surveying the same radiographs, corresponding to 0.065 pH unit precision in the range pH 4-8. We have and have also developed mechanical pin and hydraulic fluid-level sensor to amplify and display mechanical strain/bending of orthopedic implants for monitoring bone fracture healing. These sensors augment standard radiographs of tissue, bony anatomy, and hardware by also indicating local chemical concentrations and mechanical strain.

Acknowledgement: This research was supported by the following grants: NSF CHE1255535, NIH NIGMS 5P20GM103444-07, NIH 1R21EB019709-01A1, and NIH NIAMS R01 AR070305-01.

Keywords: infection, medical imaging, biosensor
Luminescent Colloidal Quantum Dots for Photonic Applications
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Colloidal semiconductor quantum dots have attracted great attentions in recent decades due to their unique optical properties including high quantum yields, tunable optical properties, and narrow-band emission. The solution processibility of these nanomaterials also enables low-cost, high throughput processes for device manufacturing. Built upon the success in controlling the size, shape, and composition of quantum dots during colloidal synthesis, researchers have employed quantum dots as the light emitters to achieve efficient electroluminescence, for potential applications in flat-panel displays and solid-state lighting. In this talk, I will present some of my group’s work on improving the manufacturability and performance of quantum dot based light-emitting devices, as well as in terms of understanding the basic operation principles. Maximum external quantum efficiencies in the range of 12-15% have been now achieved for blue/violet, green and red emitting devices with long lifetimes ~100,000 hours or higher for the green and red devices.

Bio: Jiangeng Xue is Professor of Materials Science and Engineering at the University of Florida in Gainesville, Florida, USA. He was previously a University of Florida Research Foundation Professor (2013-2016) and Associate Chair of the MSE department (2015-2017). He received his B.S. and M.S. in physics from University of Science and Technology of China (USTC), and received his M.A. and Ph.D. in Electrical Engineering from Princeton University, working in the field of organic electronics with Prof. Stephen R. Forrest. Before joining the faculty at UF he also worked as a Research Scientist at Global Photonic Energy Corporation for nearly a year. He was an adjunct professor at Zhejiang University in 2014 while he was on sabbatical leave from UF and was a visiting professor at USTC in 2012. His research interests are broadly on the science and engineering of organic and hybrid organic-inorganic electronic materials including nanostructures and energy materials. He is a recipient of a NSF CAREER Award and a Solar Energy Innovation Award from Princeton University, and was named as a Scialog Fellow by Research Corporation for Science Advancement (RCSA). His work has been funded by NSF, U.S. Department of Energy, DARPA, DTRA, Florida Energy Systems Consortium, Research Corporation for Science Advancement, as well as the industries.
Controlling the Natures of Carbon Nanodots with Ionic Liquids

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Carbon nanoparticles (carbon dots, CDs) exhibit tunable fluorescent emission property, chemical stability and favorable biocompatibility, and thus possess promising potentials in a wide range of application fields, including sensing, bio-imaging and drug delivery. It is highly desired to regulate the properties of CDs, e.g., hydrophilicity/hydrophobicity, fluorescent behaviors, biocompatibility, and cell penetration capability. For this purpose, the following practices were conducted:

1) The regulation of hydrophilicity/hydrophobicity of CDs is realized via hydrothermal preparation with 1-butyl-3-methylimidazolium hexafluorophosphate as carbon source in a H$_3$PO$_4$-ethanol medium. The hydrophilicity or hydrophobicity of CDs (or their proportions) is simply regulated by varying the H$_3$PO$_4$/ethanol molar ratio within 0-1.72, while hydrophilic or hydrophobic CDs are the solely product from H$_3$PO$_4$-BmimPF$_6$ or BmimPF$_6$-only systems;

2) The improvement on CDs biocompatibility is performed with modification by ionic liquids. Amide group functionalization of CDs is conducted via microwave irradiation. Afterwards carboxyl containing ionic liquid 1-carboxymethyl-3-methyl imidazolium bromide is coupled on the surface of Amide-CDs via covalent conjunction. Both Amide-CDs and IL-CDs exhibit abundant surface functional groups, resulting in tunable fluorescent emission feature. After modification the biocompatibility is improved significantly, facilitating cell imaging with higher level of CDs;

3) Hydrothermal treatment of ionic liquid 1-ethyl-3-methylimidazolium bromide produces hydrophobic CDs with tunable fluorescent emission and rapid cell penetration capability, originating from alkyl groups on CDs surface. CDs show excitation-dependent emission along with red-shift of maximum excitation/emission wavelength by increasing CDs concentration. CDs penetrate cell membrane via multiple pathways within 1 min, which significantly reduces sample treatment time and is preferential for avoiding sample inactivation and potential fluorescence quenching;

4) Imidazolium ILs were used to control CDs properties by sulfuric acid carbonization. Hydrophilic CDs (IL-HCDs) and organophilic CDs (IL-OCDs) were achieved simultaneously. The quantum yield of IL-OCDs is closely related with both cationic and anionic moieties in the ionic liquids, i.e., longer side chains of cations and weakly nucleophilic anions tend to produce highly fluorescent IL-OCDs. IL-OCDs serves as a favorable drug carrier with high drug loading efficiency for anticancer drug curcumin (Cur) and facilitates rapid penetration/transportation of Cur into cell interior, which significantly accelerates the apoptosis of HeLa cells.

Keywords: carbon dots, functionalization, ionic liquids

Reference
Our research interests focus on the development of advanced scanning probe microscopy (SPM) for biomedical analysis and manipulation. In this talk, the detail analysis from molecule to cell will includes: (1) Explore DNA self-assembling nanostructures and its mechanism of the thermodynamics, and develop a new room temperature method for DNA self-assembling[ref. 1 to 6]; (2) Beside, more recent works will be introduced for single molecular manipulation by DNA nanotechnology[ref. 6 and 7]; (3) Finally, I will propose our recent efforts to extend the atomic force microscopy’s application on subcellular analysis and manipulation, and focus on detection method of cancer cell biomarkers and biology mechanism of nanodrugs, which would like to provide more supporting for cancer early detection and diagnosis.

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A Single Molecule Level Detection by Nanopore Technique

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Single-molecule analytical techniques that analyze the structure, conformational change, dynamic and interaction of the analytes at single-molecule level can provide more information of molecular structure and their function or mechanism. Based on α-Hemolysin (α-HL) nanopore, we developed analytical platform for small molecule drug mechanism and thermodynamic analysis, real-time nanocluster structure identification and rapid cocaine detection in complex biofluids.

First, we developed nanopore method to analyze small molecule-biomolecule interaction mechanism and thermodynamics in single-molecule level.\(^1\) Human telomere sequence interactions with a small molecule drug pyridostatin (PDS) were analyzed. The potent stabilization effect of drug on G-quadruplex structure was demonstrated by analysis of the unraveling time of G-quadruplexes. The nanopore platform permits the efficient and accurate determination of drug affinity constants without the requirement for labeling, amplification, or varying the ligand/receptor concentration. The translocation studies and the free-energy analysis demonstrated a coordinated effect of K\(^+\) and drug on G-quadruplex stabilization. Nanopore method possesses great potential for the design and screen of anticancer drugs.

Second, we present a nanopore method to identify nanoclusters with different structures in single molecule level, by providing structure-dependent 2D dwell time-current blockage spectra and specific capture rates for the cluster translocation events. The α-hemolysin ion channel permits the discrimination of different kinds of polyoxometalate structures with atomic precision, and shows much higher sensitivity than conventional techniques in nanocluster detection. Nanocluster translocation through the nanopore was investigated with molecular dynamics simulations, which unambiguously reveal the nanocluster translocation dynamics and related the experimental results with the nanocluster structure. Besides, this sensor allows simultaneous in-situ detection of multiple nanoclusters in real-time.

Third, we constructed a label-free nanopore biosensor for rapid and highly sensitive detection of cocaine in human serum and saliva samples based on target-induced strand release strategy.\(^2\) In this bioassay, an aptamer for cocaine was pre-hybridized with a short complementary DNA. Owing to cocaine specific binding with aptamer, the short DNA strand was displaced from aptamer and translocation of this output DNA through α-hemolysin nanopore generated distinct spike-like current blockages. A wide concentration range from 50 nM to 100 µM of cocaine was obtained, with the limit of detection down to 50 nM.

**Keywords:** nanopore, single molecule analysis, thermodynamics, nanocluster, biosensor

**Reference**


**ACKNOWLEDGMENT**
This work was financially supported by National Natural Science Foundation of China.
In the postgenomic era, one expects the suite of chemical players in a brain region to be known and their functions uncovered. However, many cell-to-cell signaling molecules remain poorly characterized and for those that are known, their localization and dynamics are oftentimes unknown. We have created new approaches for assaying the chemical contents within thousands of individual brain cells. The cells of interest are scattered across a microscope slide, their exact positions determined and lastly, mass spectra are acquired at the cell positions [1]. Single cell assays allow differences in the metabolome and peptidome from supposedly homogeneous populations of cells to be explored [2]. By obtaining information from tens of thousands of individual cells, rare cells are found and unusual neurochemicals are discovered. As the method allows follow-up immunohistochemistry and capillary electrophoresis–mass spectrometry [3] on selected cells, a wealth of single cell chemical information on cell populations becomes possible. Several applications of single cell mass spectrometry are highlighted from the discovery of unusual metabolites to characterizing the neuropeptides and hormones in single cells. Our overarching goal is to uncover the complex chemical mosaic of the brain and pinpoint key cellular players in a range of physiological and pathological processes.

Fig 1. A variety of sampling approaches enable the mass spectrometry (MS) characterization of cells, including capillary electrophoresis MS, mass cytometry, microarrays for MS, MS imaging, and microMS.

Keywords: mass spectrometry, neuropeptides, capillary electrophoresis, single cell

Interfacing DNA with gold nanoparticles (AuNPs) has produced a diverse range of biosensors, imaging agents, drug delivery systems, and new materials. AuNPs are particularly attractive because of their low toxicity and unique optical, electric and catalytic properties. While many practical applications have been demonstrated, the fundamental interaction between DNA and AuNPs remains to be fully explored. Most of the previous work has been carried out on planar gold surfaces, which can be tested under essentially any buffer conditions and a diverse range of surface science tools are available. On the other hand, AuNPs have colloidal stability problems, limiting the salt concentration and other buffer conditions. Using fluorescently labeled oligonucleotides as probes, we have measured the kinetics of DNA adsorption, desorption as well as adsorption isotherm as a function of salt, pH, and temperature. An important application of such fundamental studies is the attachment of DNA to AuNPs. Electrostatic repulsion between DNA and gold and among DNA are the main barriers to achieving a high DNA density on AuNPs. Highly efficient DNA adsorption can be achieved at low pH [1]. We were able to functionalize AuNPs with thiolated DNA in just a few minutes at pH 3, whereas the traditional salt aging method at neutral pH takes more than one full day. The effect of DNA conformation in acid buffer was also found to be important [2]. Freezing was discovered to be a highly efficient way to produce conjugates and no salt or acid was required [3]. In addition to the cation part of salt, the anions are also found to be critical. For example, bromide enabled more stable conjugates than the typically used chloride salt [4]. In addition to AuNPs, adsorption of DNA by other common inorganic surfaces was also studied [5].

**Keywords:** gold nanoparticles, DNA, biosensors, bioconjugate chemistry, aptamers

**References**

Mn-based oxides with micro-nanostructures for rechargeable batteries

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Micro-nanostructures have shown promising in the application of electrochemical energy storage and conversion because of faster ion surface/interface diffusion reaction. Mn-based electrode materials such as layed LiNi_{0.6}Mn_{0.2}Co_{0.2}O_{2} and spinel CoMn_{2}O_{4} with micro-nanostructures have been synthesized via reduction-oxidation-transformation crystallization. The as-synthesized micro-nanostructures have demonstrated enhanced electrochemical performance in the application of rechargeable Li (ion/metal) batteries.

Keywords: Mn-based oxides, micro-nanostructures, layed oxides, spinels, Li batteries

Reference
Self-powered Biosensors for Cancer Diagnosis and Self-sustained Theranostic Platform for Tumor Based on Biofuel Cell

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Biofuel cell (BFC) powered self-sustained biosensors represent an external-energy-equipment-free sensing system which is capable of continuously providing precious quantitative analytical information of various analytes according to the change in the output of BFC. Recently, we developed an ultra-sensitive self-powered cytosensor for the detection of acute leukemia CCRF-CEM cells. To further multiply the detection target, we also succeeded in constructing a self-powered system which could quantify two types of cancer-related biomarkers (miR-21 and miR-141). These self-powered biosensors suggest the great promise in achieving point-of-care diagnosis. Furthermore, based on BFC, we have devised a high-compact and self-sustained theranostic platform which possessed triple cascaded “diagnosis-therapy-therapeutic evaluation” functions. The presented platform hints a sustainable cross-link between BFC and advanced theranostic, further offering guidance towards adjusting the preclinical medication to achieve preferable personalized medicine at an economical cost.

Keywords: Biofuel cell, Self-powered, Biosensors, Theranostic

Reference
Plasmonically Powered Nanoprobes for Biomedical Applications

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Designing, synthesizing and controlling plasmonic metal nanostructures with high precision and high yield are of paramount importance in optics, nanoscience, chemistry, materials science, energy and biotechnology. In particular, synthesizing and utilizing plasmonic nanostructures with ultrastrong, controllable and quantifiable signals is key to the wide and practical use of plasmonic enhancement-based spectroscopies including surface-enhanced Raman scattering (SERS), but highly challenging. Here, I will introduce the design and synthetic strategies for molecularly tunable and structurally reproducible plasmonic nanogap structures with strong, controllable and quantifiable SERS and enhanced photoluminescence signals. I will also show their potentials in addressing some of important challenges in science, and discuss how these new plasmonic materials can lead us to new breakthroughs in biotechnologies including biosensing, bioimaging and theranostic applications.

Keywords: plasmonics, nanoprobe, biosensing, SERS, surface-enhanced spectroscopy

Reference

Detection Method of Non-fluorescent Molecules for Micro/extended-nano Fluidics and Its Application

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Epigenetics is a field where regulation of DNA transcription/expression is analyzed through analysis of DNA or protein modification. Normally, millions of cells were sampled, and methylation or histone modification were analyzed. However, due to limitation of available cells, ultrasensitive analytical method is highly required, and 10-100 cell epigenome systems is a challenging target. Bulk-scale analytical tool was difficult to apply due to quite low efficiency in chemical processes.

Recently, micro/nano fluidics have progressed rapidly. Integration method and the fundamental technologies were well developed, and the superior performances were verified in analytical time, sample/reagent volume, easy to operate, and integrated devices.

Related to epigenomics, our group integrated ELISA (enzyme-linked immunosorbent assay) in a microfluidic device for the first time, and assay time was reduced to minutes scale. The sample volume was also reduced dramatically. In this presentation, utilizing our ELISA technology, we will integrate chromatin immunoprecipitation (ChIP) device for genome-wide sequencing with a next generation sequencer. 100 cells were captured in a microchannel, and cell lysis, enzyme-restriction, immunocapture, and enzyme-digestion were integrated in a single device. For process monitoring of the immunoprecipitation, detection device is required. For this, thermal lens detection (TLD) device was developed to detect nonfluorescent/fluorescent molecules in microspace.

Keywords: Thermal lens microscope, epigenetics, ChIP-seq

Reference
Molecularly Imprinted Polymers with Integrated Fluorescence as Versatile Biomimetic Sensing Matrices

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Molecularly imprinted polymers (MIPs) are an established, versatile and high-performance matrix for the selective separation or enrichment of (bio)chemical species, especially small molecules of biochemical or environmental relevance. MIPs are prepared through the polymerization of a mixture of functional monomers and cross-linkers in the presence of the template with subsequent extraction of the latter. Conceptionally, this process can be seen as mimicking in a strongly accelerated, though single-step manner a biological process such as antibody formation. Because the resulting MIPs contain cavities in their matrix that are complementary in size, shape and electronic/electrostatic or hydrogen bonding demand to the imprinted target molecule or template, these polymers are frequently termed “artificial antibodies”. Compared to natural antibodies, they are chemically and physically much more robust. Regarding sensitivity and selectivity, however, there is still a gap to bridge before MIPs can fully compete with antibodies.

Another favorable aspect that distinguishes MIPs from antibodies is that they can be endowed with an explicit function, allowing the use of MIPs in applications that require more than only an efficient binder. For instance, if specifically designed and polymerizable fluorescent indicators are integrated as functional monomers into a MIP, direct fluorescence sensing can be accomplished. Because MIPs can be prepared in a variety of different formats, their combination with miniaturized or other specific analytical techniques or sensory devices is possible, especially when the transduction mode is light. This presentation will introduce basic design considerations, challenges, limitations and the potential that lies with such sensor materials with some recent examples of our group, targeting various organic oxoanions as analytes.

Keywords: Molecularly imprinted polymers, fluorescence, anion recognition

References

Smart Interfacial Materials from Super-Wettability to Binary Cooperative Complementary Systems

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Learning from nature and based on lotus leaves and fish scale, we developed super-wettability system: superhydrophobic, superoleophobic, superhydrophilic, superoleophilic surfaces in air and superoleophobic, superareophobic, superareophilic, superoleophilic surfaces under water [1]. Further, we fabricated artificial materials with smart switchable super-wettability [2], i.e., nature-inspired binary cooperative complementary nanomaterials (BCCNMs) that consisting of two components with entirely opposite physiochemical properties at the nanoscale, are presented as a novel concept for the building of promising materials [3-4].

The smart super-wettability system has great applications in various fields, such as self-cleaning glasses, water/oil separation, anti-biofouling in interfaces, and water collection system [5].

The concept of BCCNMs was further extended into 1D system. Energy conversion systems that based on artificial ion channels have been fabricated [6]. Also, we discovered the spider silk’s and cactus's amazing water collection and transportation capability [7], and based on these nature systems, artificial water collection fibers and oil/water separation system have been designed successfully [8].

Learning from nature, the constructed smart multiscale interfacial materials system not only has new applications, but also presents new knowledge: Super wettability based chemistry including basic chemical reactions, crystallization, nanofabrication arrays such as small molecule, polymer, nanoparticles, and so on [9].

Reference:
Chemical Protein Synthesis through Ligation of Peptide Hydrazides

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Proteins are interesting molecules of life. Use of chemical methods to prepare proteins de novo may enable the studies on the proteins that cannot be made recombinantly. We discovered the ligation chemistry of peptide hydrazides and developed this chemistry into a method system, which has been widely used as a standard protocol for the chemical synthesis of proteins. Using the hydrazide method system, we have successfully synthesized proteins consisting up to 450 amino acids. Furthermore, the largest protein that we synthesized and crystallized contains 304 amino acids, which demonstrated that synthetic proteins can be folded to the fully biologically active conformations. We used the hydrazide method of chemical protein synthesis to prepare proteins with post-translational modifications for biochemistry and biophysics studies. We also synthesized D-amino acid proteins to explore the possibility of developing a new array of functional molecules for biomedical and material applications.

Keywords: Protein chemical synthesis, hydrazides

Reference
Nanoprobes for Imaging with Low Background  

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Fluorescence based sensing and imaging has been widely used and drawn great attention but suffers from high background interference.\(^1\) Photothermal sensing demonstrates wide potentials due to its long wavelength and thus low background.\(^2\) Due to their long irradiation wavelength, low background, and good photothermal conversion efficiency, semiconductor nanocrystals with near-infrared localized surface plasmon resonance (NIR-LSPR) demonstrate great potentials for biochemical sensing and photothermal therapy of tumors. We developed a facile strategy for the synthesis of Cu$_7$S$_4$ nanocrystals with excellent photothermal efficiency and long wavelength SPR peak (1500 nm). After coupling with small gold nanoparticle, the Cu$_7$S$_4$-Au heterodimers show greatly enhanced LSPR absorption in the in vivo transparent window. Via assembly and surface functionalization with $^{19}$F-moieties, these nanomaterials have been successfully utilized for photothermal imaging of latent fingerprints,\(^3\) $^{19}$F-magnetic resonance imaging guided photothermal imaging and ablation of tumors with low background and high penetration depth.\(^4\)

**Fig. 1** Multifunctional nanoprobes for highly sensitive $^{19}$F-MRI and photothermal therapy.

**Keywords:** Semiconductor nanoparticles; photothermal imaging; Localized surface plasmon resonance; $^{19}$F-magnetic resonance imaging

**References**


Artificial antibody for recognition of target bio-samples
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The recognition of target bio-samples, including peptides, proteins, and even cells is of great significance in various fields. Antibody with high specificity has been playing important roles to achieve such goals. However, the stability and the re-usability of antibody should be further improved. In our recent work, we developed various molecule imprinting based artificial antibody materials, by which the specific capture of O-GlcNAc peptide, proteins and CTC was achieved. Furthermore, aptamer functionalized materials were synthesized, and successfully applied to achieve the selective capture and quantitation of several target proteins in blood.

Keywords: artificial antibody, molecule imprinting, aptamer, protein, CTC
Nanowire Probes for Applications in Energy and Biology

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One-dimensional nanowires can be merged in nanoelectronic circuits as probes to detect electrical signals in a large variety of systems including batteries, cells, tissues and organs. Here we present two major applications of nanowire probes in the field of energy and biology. In the field of energy, specifically for batteries as electrochemical energy storage devices, we designed and fabricated on-chip single nanowire electrochemical devices for in-situ probing the direct relationship between electrical transport, structure, and electrochemical properties of the single nanowire electrode to understand intrinsic reason of capacity fading. In this device design, only one single nanowire serves as the cathode or anode. The nanowire is contacted with micro/nanoscale metal electrodes which have dual functions as current collectors during battery cycling and source/drain contacts during nanowire conductivity characterization. In the field of biology, we synthesized U-shaped, V-shaped and W-shaped kinked silicon nanowires with nanoscale localized field-effect transistors (FETs) in-situ grown at the kinked region, followed by design and fabrication of bend-up and free-standing nanowire nanoelectronic bioprobes. The small dimensions of these NW transistor probes, together with phospholipid functionalization, make it possible for stable and long-term recording of full amplitude intracellular signals with minimal invasiveness. The kinked nanowire bioprobes can successfully achieve multiplexed intracellular recordings of cardiomyocytes. In addition, we demonstrated a new concept that combines alignment and shape control to achieve large-scale and high-precision U-shaped nanowire arrays. This U-shaped nanowire arrays are expected for applications in many areas including nanobioelectronics and nanophotonics.

Keywords: nanowire probes, energy and biology

Reference
Liqiang Mai, Changjiang Scholar Chair Professor of Materials Physics and Chemistry, Distinguished Young Scholar of the National Science Fund of China, Dean for International Affairs of International School of Materials Science and Engineering at Wuhan University of Technology. He received Ph.D. degree from WUT in 2004 and carried out postdoctoral research in Prof. Zhonglin Wang's group at Georgia Institute of Technology (2006-2007). He worked as an advanced research scholar in Prof. Charles M. Lieber's group at Harvard University (2008-2011) and Prof. Peidong Yang’s group at University of California, Berkeley (2017).

Semiconducting Quantum Dots for Artificial Photosynthesis: Solar-to-Hydrogen Conversion

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With the increasing concern over the global energy crisis and the greenhouse effect caused by carbon dioxide emission, the development of carbon-neutral and renewable-energy solutions has attracted considerable interest in both the scientific and industrial communities. Nature long ago figured out how to use photosynthetic complex to capture sunlight and then to store its energy in a chemical form. Artificial photosynthesis is the idea that we might be able to create energy and other useful thing from sunlight, water and carbon dioxide, as plants do. In this presentation, we will compile the following three stories to illustrate a few approaches that may be useful in the design of artificial photosynthetic systems for chemical transformation.(1) Artificial photosynthetic systems for hydrogen evolution by [FeFe]-hydrogenases mimics; (2) Artificial photocatalysts made by earth-abundant metal salts and quantum dots in situ under visible light irradiation; (3) Artificial quantum dots photocathodes for hydrogen evolution by water-splitting under visible light irradiation.

Keywords: Quantum Dots; Artificial Photosynthesis; Solar Energy Conversion; Hydrogen Evolution;

Reference
Currently, measurements such as biomarker analysis in toxicology studies are most offline and negatively impacted by the method sensitivity. Here, we report a system called dLABer that integrates living animals, breath sampling, microfluidics, and biosensor for real-time tracking the breath-borne biomarkers. Our data showed that the dLABer was able to detect and report the differences with an ultra-sensitivity among breath-borne inflammation agent interleukin-6 (IL-6) levels from rats injected with the same amount of ambient particulate matter (PM) but from different sources. The results from the dLABer system were further validated by analyzing the same breath samples using enzyme-linked immunosorbent assay (ELISA). In addition, the blood-borne IL-6 levels analyzed using ELISA from the different PM-injected rats and the PM toxicity by dithiothreitol (DTT) also agreed well with those breath-borne results from the dLABer system. Video recordings further verified that rats exposed to PM with higher toxicity (DTT) as revealed by the dLABer appeared to be less physically active. All the data here suggested that the dLABer system can be used to real-time monitor breath-borne biomarkers with an ultra-sensitivity. Here, we used rats and PM exposure for validating the dLABer, and in the future the system can be also used to detect the biomarkers from humans in various scenarios, e.g., taking medications and bedside disease monitoring. This work has developed a frontier method that is expected to revolutionize the pollutant health effects studies as well as many bed-side breath-borne disease diagnosis and monitoring.

**Keywords:** dLABer, Biomarker, PM, Toxicity, Biosensor, Real-time, Disease monitoring
In Vitro Reconstitution of Postsynaptic Density Micro-reaction Compartments

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Synapses are semi-membraneless, protein-dense, sub-micron chemical reaction compartments responsible for signal processing in each and every neuron. Proper formation and dynamic responses to stimulations of synapses both during development and in adult are fundamental to functions of mammalian brains. There are not any identical ones among trillions of synapses in a human brain. We used a biochemical reconstitution approach to show that, both in solution and on supported membrane bilayers, multivalent interaction networks formed by major excitatory postsynaptic density (PSD) scaffold proteins led to the formation of PSD-like assemblies via phase separation. The reconstituted PSD-like assemblies can cluster receptors, selectively concentrate enzymes, promote actin bundle formation, and expel inhibitory postsynaptic protein. Additionally, the condensed phase PSD assemblies have features that are distinct from those in homogeneous solutions and fit for synaptic functions. Thus, we have built a molecular platform for understanding how neuronal synapses are formed and dynamically regulated.
Structural basis of pre-tRNA processing by RNase P

Ming Lei

Ribonuclease P (RNase P) is a universal ribozyme in all three kingdoms of life responsible for processing the 5’ end of precursor tRNA. Here we report the first atomic structure of eukaryotic RNase P holoenzyme from Saccharomyces cerevisiae at a 3.48-Å resolution. The RNA component of yeast RNase P adopts an extended single-layered conformation that maintains a central helical core, but lacks most of the long-range RNA-RNA interactions that are essential for structural stability in bacterial RNase P. Remarkably, the protein subunits together form a hook-shaped architecture that tightly wraps around the RNA and stabilizes it in an active conformation. Consistent with the structure, molecular dynamics simulation reveals an obvious stabilizing effect on the RNA by the proteins. Overall, our results provide the first atomic structure of eukaryotic RNase P and explain how the structural roles of bacterial RNA elements are delegated to the protein components in eukaryotic RNase P.
Dynamic, Responsive Nanomaterials: Utility as In Vivo Delivery Vehicles and Characterization by Liquid Phase Electron Microscopy

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The goal of targeted therapeutics and molecular diagnostics is to accumulate drugs or probes at the site of disease in higher quantities relative to other locations in the body. To achieve this, there is tremendous interest in the development of nanomaterials capable of acting as carriers or reservoirs of therapeutics and diagnostics in vivo.[1] Generally, nanoscale particles are favored for this task as they can be large enough to function as carriers of multiple copies of a given small molecule, can display multiple targeting functionalities, and can be small enough to be safely injected into the blood stream. The general goal is that particles will either target passively via the enhanced permeability and retention (EPR) effect, actively by incorporation of targeting groups, or by a combination of both.[2] Nanoparticle targeting strategies have largely relied on the use of surface conjugated ligands designed to bind overexpressed cell-membrane receptors associated with a given cell-type.[3] We envisioned a targeting strategy that would lead to an active accumulation of nanoparticles by virtue of a supramolecular assembly event specific to tumor tissue, occurring in response to a specific signal. The most desirable approach to stimuli-induced targeting would be to utilize an endogenous signal, specific to the diseased tissue itself, capable of actively targeting materials introduced via intravenous (IV) injection. We present the development of nanoparticles capable of assembling in vivo in response to selective, endogenous, biomolecular signals. For this purpose, we utilize enzymes as stimuli, rather than other recognition events, because they are uniquely capable of propagating a signal via catalytic amplification. We will describe the preparation of highly functionalized polymer scaffolds utilizing ring opening metathesis polymerization, and their development as drug carriers capable of targeting tissue via a new mechanism. Furthermore, we will describe new methods and approaches for characterizing this kind of dynamic material at the nanoscale, including by liquid cell transmission electron microscopy.

References:
Linking Nanotechnology, Photonics, Biology, and Nuclear Technology
to Impact Biomedical Engineering and Nanomedicine

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The major breakthroughs required to meet 21st century technical challenges across areas of top global priority, including alternative energy, healthcare, environmental monitoring, information technology, and world security, will be achieved through convergence of science. This talk will discuss how chemistry, physics, engineering, and biology can be integrated to link nanotechnology with photonics, biotechnology, and nuclear technology to create and apply multifunctional nanomaterials with optimized optical, magnetic, thermal, radioactive, and biologic properties for numerous applications in Biomedical Engineering and Nanomedicine.

Our research applies biophotonics to nanomedicine, using targeted optical nanoprobes for bioimaging, sensing, and light-guided and light-activated therapy for cancer, infectious diseases, drug addiction, and brain diseases1-3. A major direction in brain research, pursued in our lab is neurophotonics, where we apply photoresponsive materials for functional mapping of the brain using optical and photoacoustic imaging. We have also demonstrated remote and noninvasive optogenetic stimulation of brain activity using near-IR absorbing optical nanotransformers that can provide an effective intervention/augmentation strategy to enhance the cognitive state. These technologies lay a foundation for a futuristic vision of super human capabilities. An exciting emerging direction in our research is development of nuclear nanomedicine and nano-radiopharmaceuticals for diagnostics and therapy. The lecture will conclude with a discussion of future outlook and new opportunities in these fields.

References:
Short Bio of Paras N. Prasad

PRASAD currently holds the unique multidisciplinary position of SUNY Distinguished Professor of Chemistry, Physics, Electrical Engineering, and Medicine (four departments spanning three schools), as well as the Samuel P. Capen Chair of Chemistry, and Executive Director of the multidisciplinary Institute for Lasers, Photonics and Biophotonics, which he founded in 1999. His pioneering contributions in interdisciplinary chemical research at the interface of photonics, nanotechnology, and biomedicine have broadly impacted healthcare, energy, and optical technologies. Scientific American named him among the world's top 50 science and technology leaders. He has authored more than 800 scientific papers; four field-defining monographs, widely used in teaching worldwide, in nonlinear optics, biophotonics, nanophotonics, and nanomedicine; eight edited books; and numerous patents. He introduced and advanced new frontiers of organic nonlinear optics, nanophotonics, biophotonics and nanomedicine. His many awards for research excellence include the Morley Medal and Schoellkopf Medal from the American Chemical Society; Guggenheim Fellowship; Sloan Fellowship; Western New York Health Care Industries Technology/Discovery Award; SUNY Excellence in the Pursuit of Knowledge award; UB’s first Innovation Impact award; UB President’s Medal; SPIE’s highest honor, the President’s Gold medal; Optical Society of America’s Michael Feld Biophotonics award; IEEE’s Pioneer Award in Nanotechnology; and the American Chemical Society’s Peter Debye Award. He is a fellow of the APS, OSA, SPIE, and IEEE and listed among Thompson Reuters “Highly Cited Researchers”. He has Honorary Doctorates from KTH in Sweden, the Aix-Marseille University in France, MEPhI in Russia, and Federal University of Pernambuco in Brazil. Globally, his technologies have produced 9 spin-off companies including publicly-traded Nanobiotix, now in advanced clinical trials for cancer therapy.
Nanotechnology Approaches to Cellular Therapies

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We introduce biomolecular payloads into cells for gene editing at high throughput for off-the-shelf solutions targeting hemoglobinopathies, immune diseases, and cancers. We circumvent the need for viral transfection and electroporation, both of which have significant disadvantages in safety, throughput, cell viability, and cost. Mechanical deformation can make cell membranes transiently porous1 and enable gene-editing payloads to enter cells. These methods use specific chemical functionalization and control of surface contact and adhesion in microfluidic channels. Likewise, penetration of reproducibly nanomanufactured, loaded sharp features can introduce these packages into individual or many cells.2 We discuss our progress with these approaches and the methods that we use to quantify success.

Keywords: nanoscience, nanotechnology, gene editing, microfluidics

Reference
Bioorthogonal kinase modulation and pro-drug activation in living systems

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Abstract: Employing small molecules or chemical reagents to modulate the function of an intracellular protein of interest, particularly in a gain-of-function fashion, remains highly desired but challenging. In this talk, I will introduce a “genetically encoded chemical decaging” strategy that relies on our developed bioorthogonal cleavage reactions to control protein activation in living cells. These reactions exhibited high efficiency and low toxicity for chemical decaging of the masked-lysine residue on intracellular proteins, which is complementary to the previously used photo-decaging reactions. We are currently employing this method to block specific kinase’s activity in living cells, which allowed the subsequent gain-of-function study of individual kinase within the intracellular signaling transduction network. Our efforts on exploring the therapeutic potential of these novel reactions for pro-drug activation will also be discussed.

References:
Professor Peng Chen is now the Chairman of Department of Chemical Biology at Peking University. He obtained BS degree in Chemistry at Peking University in 2002 and Ph.D in Chemistry at The University of Chicago in 2007. After a postdoctoral training at The Scripps Research Institute, he started his independent career as an Investigator at Peking University in July 2009 and has been promoted to Full Professor with tenure in 2014. His research focuses on developing and applying novel chemistry tools to investigate protein-based interactions and activities in living cells. His lab is best known for the creation of versatile genetically encoded photocrosslinkers for studying protein-protein interactions, as well as the development of bioorthogonal cleavage reactions for protein activation in living systems. He received many awards including NSFC Distinguished Young Scholar Award (2012), RSC Chemical Society Review Emerging Investigator lectureship (2014), The Chemical Society of Japan Distinguished Lectureship Award (2015), Young Scientist Award from Ministry of Education in China (2016), Tan Kah Kee Young Scientist Award (2016), and Society of Biological Inorganic Chemistry Early Career Award (SBIC award, 2017).
Ligand-Guided Selection (LIGS): A SELEX Variant to Develop Aptamers Against Cell-surface Markers

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Aptamers are evolved using a combinatorial screening method called Systematic Evolution Exponential enrichment (SELEX). To increase the applicability of aptamer selection, it is necessary to develop of methods to select aptamers that could specifically recognize predetermined epitopes in their endogenous state with no prior- or post SELEX sample manipulations. To this end, we report on a new strategy to identify highly specific aptamers against a predetermined epitope of a cell-surface target termed “Ligand-guided-Selection”. The iterative process in conventional SELEX is designed to outcompete low-affinity binders through a competitive process whereby high affinity binders move on through the selection process. LIGS strategy exploits this step to isolate highly specific DNA aptamers against a predetermined target. In order to identify specific aptamers we used a naturally occurring stronger and highly specific bivalent binder, a monoclonal antibody (mAb) interacting with its cognate epitope to out-compete aptamers from a partially enriched SELEX pool against cells expressing the same epitope. This study will introduce a new method of selecting synthetic nucleic acids ligands against cell-surface markers at their endogenous state.

Keywords: Cell-SELEX, Aptamer, LIGS
Brainsmatics--Deciphering Genetically Defined Cell Types and Connectome with Brain-wide Positioning System.

Qingming Luo

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Deciphering the fine morphology and precisely positioning the neurons and neural circuits are crucial to enhance our understanding of brain function and diseases. Traditionally, we have to map brain images to coarse axial-sampling planar reference atlases to orient neural structures, which might fail to orient neural projections at single-cell resolution due to position errors resulting from individual differences at the cellular level. In last one and half decade, my lab developed a Micro-Optical Sectioning Tomography (MOST) and several types of fluorescence MOST (fMOST), which is a novel combination of the microscopic optical imaging and the physical sectioning to obtain the tomographic information of a whole brain with sub-micron voxel resolution. In the first part of my talk, I will introduce the principles of Brain-wide Positioning Systems (BPS) which refers to MOST/fMOST serial techniques. In the second part of my talk, I will demonstrate how to brain-widely position the labelled neurons and neuronal networks, including whole-brain samples preparing, whole-brain optical imaging as well as massive brain-image processing and analyzing. The unique features of BPS include 1) robust absorption/fluorescence imaging, 2) multi-color imaging, 3) submicron voxel resolution for a single cm-size whole mouse brain, 4) automatic in sectioning, imaging and data acquisition, 5) no registration needed for 3-D imaging, 6) extensible for 3-D large scale imaging, potentially to 10×10×10 cm³. Based on BPS, we have acquired the first 3D structure atlas of whole mouse brain at single-neuron resolution; achieved tracing axonal pathways in the mouse brain without interruption for the first time; firstly dissected neural structures with anatomical annotation at single-neuron resolution; revealed the mechanism of fluorescent signal change in resin-embedded sample; realized the automatic tracing and reconstruction of neuronal populations with dense dendrites. We propose a new term: BRAINSMATICS, which refers to the integrated, systematic approach of measuring, analyzing, managing and displaying brain spatial data with unprecedented single-neuron resolution. The serial BPS have the advantages of high resolution, high throughput and long-time stability. With the brain-spatial information of neuron types, neural circuits, vascular networks and 3D fine brain atlas, we believe that brainsmatics makes it possible to better decipher genetically defined cell types and connectome.

Keywords: Brainsmatics, Brain-wide Positioning Systems, cell type, connectome
Ultrasensitive Tracking Basal Hydroxyl Radicals in Living Cells by Fluorescence Amplification Using Cell Self-Power

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Signal amplification is critical for detecting low levels of biological species. Most previous methods rely on polymerization of nucleic acids but manipulating them in living cells is challenging due to complex reaction conditions, the need of external enzymes, or a long reaction time. Herein, a new signal amplification concept called cytomatrix-assisted in situ fluorescence amplification (CAFA) is proposed (Fig. 1). CAFA takes the cytoplasmic components rather than exotic catalytic power for signal amplification enabling it to operate in living cells. To make a biosensor using CAFA for hydroxyl radicals (‘OH), we screened a cytomatrix-activated dye named PBF 1, whose fluorescence is enhanced by over 28-fold via binding to cellular proteins. PBF 1 is entrapped inside a mesoporous silica nano-container and its fluorescence is quenched by a designed DNA/PTAD signal switch. The DNA/PTAD-based switch is opened by ‘OH cleavage, to release and thus light up fluorescence of the quenched PBF1. Moreover, the fluorescence of the released PBF1 is further amplified by cytoplasm proteins. This cascade signal amplification enables ultrasensitive fluorescence activation imaging of intracellular basal and stimulated OH· levels and fluctuation with a picomolar detection limit (Fig. 2). To the best our knowledge, this is the first effort to use cellular proteins for amplifying detection signals inside living cells, which will provide a new dimension to current methodologies for low-abundance biomarkers discovery and regulation for chemical biology and medical diagnostics.

Keywords: Fluorescence; Signal Amplification; Protein Assisted; H₂O₂

Reference
Advanced Miniature Biofuel Cells

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Biofuel cells (BFCs) use enzymes as catalysts to oxidize their fuels. Miniature versions have been excited by scientists because they are portable and have high efficiency. Here, a paper-based mediator-less and compartment-less BFC has been assembled, which can harvest energy from a wide range of commercial beverages containing glucose, providing a simple approach to fabricate low-cost and portable power devices. Further an origami-style biofuel cell with manganese oxide cathode and an enzymatic anode is assembled simply by hand and use cheap raw materials. The miniature biofuel cell prepared can generate energy from soft drinks. Based on inhibition effect of toxins to enzyme activity in BFCs, the miniature biosensor was fabricated successfully for detecting CN\(^-\) in endogenous biological cyanide, and also for detecting trace Hg\(^{2+}\) in real water samples, respectively.

A self-powered wearable sensor based on a photoelectric biofuel cell has been introduced to detect the perspiration lactate and monitor the ambient illuminance simultaneously. This novel design may provide a wide range of smart and exciting wearable electronics.

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Bio-Inspired Synthesis and Self-Assembly of Functional Materials

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There is a rich and long history of gaining inspiration from nature for the design of practical materials and systems. Biominerals are well-known composites of inorganic and organic materials in the form of fascinating shapes and high ordered structures, which exist in Nature, for example, pearl, oyster shells, corals, ivory, sea urchin spines, cuttlefish bone, limpet teeth, magnetic crystals in bacteria, and human bones, created by living organisms. During the past few decades, it has been one of the hottest research subjects in materials chemistry and its cutting-edge fields to explore new bio-inspired strategies for self-assembling or surface-assembling molecules or colloids to generate materials with controlled morphologies, unique structural specialty, and complexity. Although the properties of nanomaterials are frequently superior to those of their bulk counterparts, translating the unique characteristics of nanoscale components into macroscopic functional materials still remains a challenge.

This lecture will report our recent advances on bio-inspired synthesis of a family of inorganic micro-/nano- structural materials and their macroscopic scale assemblies, including bio-inspired molecule induced synthesis of micro-/nano-inorganic materials, bio-inspired interfacial assembly of macroscopic assemblies and functionalization. Especially, we will report our recent effort on how to realize the bulk production of synthetic nacre spanning all the length scales either by predesigned matrix-directed mineralization process or a bottom-up self-assembly process. These macroscopic nanoparticle assemblies are emerging as a new material system, showing enormous application potentials in diverse fields.

Keywords: bio-inspired synthesis, inorganic materials, nanoscale building blocks, self-assembly, application.

Reference
Silicon Nanostructures for Biomedical and Energy Applications

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Silicon nanostructures have a great potential for wide-ranging applications due to their many attractive properties, such as biocompatibility, earthly abundance, and unique electronic and optical properties, arising from small size and large surface-to-bulk ratio. The attractive properties and a growing interest in their synthesis and applications have fueled extensive investigations of silicon nanostructures in recent years. In this talk, I shall introduce our efforts on the development of silicon nanostructures to serve as a new, powerful platform for biomedical applications, including bioimaging and cancer therapy. I shall also describe our various approaches to exploit the unique properties of Si nanostructures for solar energy conversion. This talk will highlight our systematic research on Si nanostructures for biomedical and renewable energy applications.

Key words: Silicon nanostructures, Biomedical, Solar energy
Biosensing Analysis for Tumor Markers, Drug Delivery and Treatment

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At present, the specificity and sensitivity of tumor markers detection methods are not high enough, which can lead to false positive and false negative. So we need to build highly sensitive detection methods to achieve key technology innovation. We take tumor cells and related active molecules as the research object, according to carry on miRNA, protein marker detection and construction of functionalized three helix molecular probe and rolling circle replication strategy and chemiluminescence resonance energy transfer imaging method. Intracellular miRNA imaging analysis is achieved. The detection of DNA methylation was realized by using the ECL resonance energy transfer of gold nanoparticles and quantum dots, and the color change of the gold nanoparticles and the surface enhanced raman scattering of the mesoporous silica by click reaction. A variety of graphene family peroxidase was constructed to detect tumor marker CEA, cell surface carbohydrate and tumor cells. Using the lock core to construct a double stranded structure, nano channel to differentiate miRNA single base mismatch was developed. On the basis of previous work, the integration of drug loading and treatment was studied by the magnetic RNA nanoprobe.

Keywords: Chemical sensing, Tumor markers, Drug delivery, Treatment

Reference
Nanofluidics Device for Total System Integration of Single Cell Protein Analysis

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Single cell analysis is one of the most active topics of bioscience and engineering. However, almost all of the analytes are nucleic acids. Proteins are also important target for single cell proteomics, metabolomics, pathology, and so on. But protein cannot be amplified chemically and much more complicated chemical processing is needed. Therefore, single cell protein analysis requires total system integration of chemical processing, and it has been still a very challenging topic.

We have developed pressure driven microfluidics from the very early stage of microfluidics in the early 1990's. We established the basic concept and method of total integration of entire chemical processes for analysis, synthesis, cell experimental protocol, and so on. The key concept is micro unit operation MUO and continuous flow chemical processing CFCP. Our original ultra-sensitive detector thermal lens microscope TLM is also a powerful readout device for non-fluorescent target molecules. These methods innovated the microfluidics and established the bases of today's biomedical microfluidics like immunoassay, extraction, cell culture, organs on chip, and other applications in the 1990's. Recently, we have pioneered nanofluidics since beginning of the 2000's, carrying the same methodologies as microfluidics, nano unit operation NUO and CFCP. We realized femto liter fluid control, and femto liter NUO and CFCP as well single/countable molecule detection by the modified TLM are already available.

We applied those original methodologies to total integration of the complicated chemical processing for single cell protein analysis. In this lecture, an example of femto liter ELISA for the samples from single cell will be introduced.
A fluid (a gas or a liquid) adsorbed in a porous material can behave very differently from its bulk counterpart. Capillarity is a popular phenomenon induced by the confinement of a liquid in a tiny pore. Early investigations of capillary phenomena were undertaken by Young and Laplace. The advent of various synthesized materials with nanopores and their wide applications have provided new impetus for studying fluids in confinement since our current understanding is still incomplete. From a large number of Monte-Carlo simulations, we found a scaling relation which allows for connecting some thermodynamic properties of a confined fluid to the bulk ones. Upon rescaling adsorbed-fluid density, the adsorption-isotherms for many different confining environments collapse to the corresponding bulk curve. We reveal also the intimate connection of the reported scaling relation to Gibbs theory of inhomogeneous fluids and morphological thermodynamics. The advance in our understanding of confined fluids, gained from this study, opens also attractive perspectives for circumventing experimental difficulty for directly measuring some fluid thermodynamic properties in nanoporous materials.

**Keywords**: Fluid adsorption in porous materials, Nanopores, Monte-Carlo simulation.
A full understanding of the molecular basis of diseases depends on the development of molecular probes able to recognize disease targets of interest. Until very recently, such tools have been absent from the clinical practice of medicine. The newest molecular probe, and one that holds most promise, is a new class of designer nucleic acids, termed aptamers, which are single-stranded DNA/RNA able to recognize specific targets, such as single proteins and even small molecules. Recently, we applied a simple, fast and reproducible cell-based aptamer selection strategy called Cell-SELEX which uses whole, intact cells as the target for aptamer selection. This selection process then generates multiple aptamers for the specific recognition of biological cells, but without the need for prior knowledge about the signature of target cell-surface molecules. The selected aptamers have dissociation constants in the nanomolar to picomolar range. Thus far, we have selected aptamer probes for many different diseases, and used them to carry out studies at the vanguard of biomedical science, including ultrasensitive detection of tumors, molecular imaging, targeted drug delivery, and, most critically, cancer biomarker discovery.

References

Tracking β-galactosidase activity in vivo

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Development of fluorescent probes for on-site detection and long-term tracking of specific biomolecules or cells is particularly desirable for disease diagnosis and therapy. However, most of reported fluorescent probes tend to migrate across the cell membrane or suffer from aggregation-caused quenching (ACQ) effect, resulting in short imaging time, low signal fidelity, and poor spatiotemporal resolution. Here we report a β-galactosidase (β-gal)-responsive aggregation-induced emission (AIE) fluorescent probe QM-βgal composed of a hydrophilic enzyme-triggered moiety (β-galactopyranoside group) and a hydrophobic AIE-active fluorogen (quinoline-malononitrile derivative, QM-OH), which enables real-time in situ measurement and long-term trapping of β-gal activity in living systems. The probe is virtually nonfluorescent in aqueous media, but its solubility can be changed when activated by β-gal, yielding a highly fluorescent nanoaggregates as a result of AIE process. QM-βgal shows a large Stokes shift (∼125 nm), excellent selectivity over other potentially interfering species, and low cytotoxicity, allowing for in situ visualizing endogenous β-gal activity in living cells with high spatiotemporal resolution. More importantly, taking advantage of its improved intracellular retention, we further exemplify QM-βgal for long-term (∼12 h) tracking of β-gal-positive ovarian cancer cells for the first time, which is of great value and desirable for biomedical study and disease diagnostics. As compared to reported β-gal probes, our system provides new insights into the development of effective tools for long-term tracing of enzyme activity in practical applications.

References

Seeing molecular vibrations: chemical imaging for biomedicine

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Innovations in light microscopy have tremendously revolutionized the way researchers study biological systems. Although fluorescence microscopy is currently the method of choice for cellular imaging, it faces fundamental limitations such as the bulky fluorescent tags and limited multiplexing ability in the era of “omics”. To address these challenges, I will present two chemical imaging strategies, respectively. First, we devised a Bioorthogonal Chemical Imaging platform suited for probing the dynamics of small bio-molecules, which cannot be effectively labeled by bulky fluorophores [1]. This scheme couples the emerging stimulated Raman scattering microscopy with tiny and Raman-active vibrational probes (e.g., alkynes and stable isotopes). Exciting biomedical applications such as imaging fatty acid metabolism related to lipotoxicity, glucose uptake and metabolism, drug trafficking, protein synthesis in brain, DNA replication, protein degradation, RNA synthesis and tumor metabolism will be presented. Second, we invented a super-multiplex optical imaging technique [2]. We developed electronic pre-resonance stimulated Raman scattering (epr-SRS) microscopy, achieving exquisite vibrational selectivity with high versatility and sensitivity. Chemically, we created a unique vibrational palette consisting of novel dyes, each displaying a single epr-SRS peak in the cell-silent spectra window. Up to 24 resolvable colors are currently achieved with potential for further expansion. This super-multiplex optical imaging approach promises to facilitate untangling the intricate interactions in complex biological systems, and can also find broad applications in photonics and biotechnology in general.

Keywords: Raman microscopy, stimulated Raman scattering, chemical imaging, multiplex imaging

References

It is a long dream to develop two-dimensional (2D) conjugated polymers due to their unique 2D structure and prominent optoelectronic properties for devices and circuits. Here, we make this breakthrough to present a novel 2D conjugated polymer single crystals at centimeter-sized scale and atomic thin. It exhibit perfect sp²-carbon and sp²-sulfur conjugated periodic structure with bandgap of ~0.8 eV, displaying intrinsic 2D transporting characteristics with conductivity and sheet conductance at room temperature of 812 S cm⁻¹ and 163 μS cm⁻², respectively. Moreover, high charge carrier mobilities of the 2D conjugated polymer crystals are observed with Hall mobility up to 980 cm²V⁻¹s⁻¹ approaching silicon single crystals at room temperature.

**Keywords:** 2D, conjugated polymer, Single crystals, mobility
Sensing and tracking molecular events in live cells

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Abstract: Seeing the molecular events in living cells is of great significance in study of single cell biology and precision medicine. This presentation is a brief review of the research progress in 1) tracking single viral particles or genes in living cells, and 2) construction of molecular biosensors for visualization of molecular interactions in live cells. Technical challenges will be also discussed.
Abstract: High-performance computers face the challenge of high energy efficiency in the field of supercomputing. To address this challenge, researchers have innovated the heterogeneous parallel architectures such as GPU/CPU, which substantially improves the computing density and energy efficiency. This improvement provides a powerful computing engine for the rise of artificial intelligence. Meanwhile, the high integration of human, machine and things generates big data, which further provides sufficient material base for the rapid development of artificial intelligence. On the other hand, artificial intelligence and big data applications are also driving the differentiation of high-performance computer morphology, such as cloud computing centers, data centers, and smart accelerator clusters. With the popularization of artificial intelligence applications, they will definitely lead the development of high-performance computers, forming the trend of co-development of big computing, big data, with strong artificial intelligence.
Chemical Biology of Nucleic Acid

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Researches in my group are focus on studying the chemical biology of nucleic acids. We are studying the function of nucleic acids (DNAzyme, recognition), structures of nucleic acids (G-quadruplex DNA, Z-DNA, RNA, Methyl DNA) and clinical application (DNA cross-links, telomerase inhibitors, miRNA detection, methyl DNA detection, SNP) of nucleic acid by small molecule regulation. In my talk, I shall present our recent progress in the studies of chemical epigenetic modification.

Selected Publications:
Noncanonical Self-Assembly of Multifunctional DNA Nanoflowers for Biomedical Applications

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Watson–Crick base-pairing mediated DNA self-assembly technology has been extensively explored for the construction of various functional nanostructures, and widely applied in versatile research fields such as nanophotonics, materials, and synthesis biology. However, their biomedical application is still challenging due to their poor stability in physiological environment with lots of nucleases and low salt concentration. To solve this problem, we developed a noncanonical self-assembly of multifunctional DNA nanostructures, termed as DNA nanoflowers (NFs), and explored their biomedical applications. These NFs were assembled from long DNA building blocks generated via rolling circle replication (RCR) of a designer template \[1-2\]. Instead of Watson–Crick base-pairing between DNA strands, a mechanism involved in liquid crystallization and dense packaging of building blocks contributed to the assembly of NF, thereby avoiding the conventional complicated DNA sequence design. More importantly, NFs were exceptionally resistant to nuclease degradation, denaturation, or dissociation at extremely low concentration, which made them ideal for biomedical applications. NF sizes were readily tunable in a wide range, by simply adjusting assembly time and template sequences, or via introducing ferrocene-based hydrophobic interactions. By rational design, NFs can be easily incorporated with myriad functional moieties such as aptamers, bioimaging agents, and drug loading sites. These multifunctional NFs have been successfully applied for versatile biomedical applications \[1-4\], including selective cancer cell recognition, multiplexed cellular imaging, circumvention of multidrug resistance, as well as targeted and controlled anticancer drug delivery, and so on.

References:

Highly Photostable Fluorescent Polymer Dots for Super-resolution Stimulated Emission Depletion Imaging

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Stimulated emission depletion (STED) nanoscopy is an emerging super-resolution imaging technique which enables high spatiotemporal characterization of cellular structures and dynamics. However, its current application is limited by the lack of photostable fluorophores which can endure strong STED illumination, since the laser power of STED beam is generally several hundred folds higher than that in the confocal microscopy. Moreover, the lateral spatial resolution of STED nanoscopy is theoretically dependent on STED beam intensity, with a higher intensity resulting in a better resolution. Therefore, photostable fluorophores are urgently desired for the wide application of STED imaging. We designed and synthesized a new type of 40nm-sized conducting polymer dots (Pdots) with excellent photochemical properties, including bright fluorescence, large Stokes shift and easy surface functionalization for biomolecular labeling. Importantly, the Pdots showed superior photobleaching resistance compared with the commonly used STED fluorophores, fluorescent beads, and previously reported other new STED nanoparticle probes. Imaging of individual Pdots has been realized with a super-resolution of 70 nm, and a long-term (2 hours) continuous STED imaging of cellular Pdots has been achieved. Our results demonstrate the promising potential of developing Pdots as a new class of STED nanoprobe.

Keywords: fluorescence imaging, super-resolution imaging, fluorescent probe, semiconducting polymer dots, STED
Targeted delivery of biologics

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Abstract: 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 bio-inspired nanoparticles with for targeted delivery of biologic therapeutics.

Fig. 1 Schematic illustration of multivalent biomimetic nanostructures for targeted siRNA delivery to tumors.

Keywords: biologics, targeting, cancer, intracellular, delivery

Reference
[1] Nature Biomedical Engineering 2018 https://doi.org/10.1038/s41551-018-0214-1
Click Chemistry-Assisted Functional Proteomic Profiling

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The complexity of human proteome is dictated by alternative splicing, post-translational modifications, protein-protein interactions, and subcellular location. Selective enrichment of sub-proteomes with specific functions is crucial for proteomic profiling. In complementary to traditional affinity purification methods such as antibody-based pull-down, biorthogonal chemistry (e.g., click reaction) has emerged as a powerful tool for functional proteomic studies. In this talk, I will present two examples, click chemistry assisted profiling of O-GlcNAcylated proteins and RNA-binding proteins (RBPs).

O-GlcNAc (O-linked N-acetylglucosamine) modification is a non-canonical form of protein glycosylation, which occurs intracellular and is dynamically regulated, which regulates many important biological processes. How O-GlcNAc affects protein stability remains to be investigated at the proteome level. We developed a time-resolved quantitative proteomic strategy based on click-labeling to analyze the turnover dynamics of O-GlcNAcylated proteins. Interestingly, a subset of O-GlcNAcylated proteins are hyper-stable, exhibiting minimal removal of O-GlcNAc or degradation of protein backbones. The hyper-stable population included three core proteins of box C/D small nucleolar ribonucleoprotein complexes (snoRNPs), fibrillarin (FBL), NOP56, and NOP58. Our studies showed that O-GlcNAcylation stabilized these proteins and regulated snoRNP assembly. Blocking O-GlcNAcylation on FBL altered the 2’-O-methylation of ribosomal RNAs, and impaired cancer cell proliferation and tumor formation in vivo. These results reveals stable O-GlcNAc as an important regulatory mechanism for stabilizing proteins.[1]

RNAs, including mRNAs and noncoding RNAs, usually exist in the cells in the form of RNA-protein complexes. Lots of efforts have been made on profiling mRNA-binding proteins (mRBPs). However, comprehensive identification of coding and noncoding RBPs remains challenging. We developed a click chemistry-assisted RNA interactome capture (CARIC) strategy, which combines metabolic labeling of RNAs with an alkynyl uridine analog and in vivo RNA-protein photocrosslinking. Subsequent click reaction with azide-biotin and affinity enrichment enables genome-wide proteomic profiling of RBPs. In HeLa cells, we identified 691 RBPs. Because CARIC captures RBPs bound to both mRNAs and noncoding RNAs, the obtained CARIC RBP list provides a valuable resource for studying the posttranscriptional gene regulation network.[2]

Reference


Plasmon enhanced spectroscopic and electrochemical detection of biomolecules

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The localized surface plasmon resonance (LSPR) arises from the collective oscillation of conduction electrons of metal nanostructures which can be used to monitor recognition events of biomolecules at single nanoparticles. The enhanced electric field around the nanostructures due to LSPR will significantly enhance the Raman scattering, fluorescence and IR spectra, which enable the realization of single molecule detection. In addition, the LSPR will excite high-energy electron-hole pair (referred to as “hot electrons” and “hot holes”) emerging on metal surface. The energetic charges will considerably affect the electrochemical reactions occurring at the nanoparticles. When the plasmonic metallic nanostructures are coupled to other substrates, for example, the semiconductor (i.e., TiO$_2$, MoS$_2$), the plasmon-excited hot electron-hole at nanoparticle surface can communicate with the conductance and valence bands of the semiconductors, resulting in variation in electro/photocatalytic activity. In this talk, we will start with the study on the possibility of LSPR for monitoring biomolecules and their recognition events at single nanoparticles. Then, we report the LSPR enhanced IR for biosensing. In the third part, we will show how the LSPR accelerates electrochemical reactions of electroactive biomolecules such as glucose on gold nanoparticles and hydrogen evolution reaction at molybdenum disulphide nanosheets. Based on the plasmonics accelerated electrochemical reactions (PAER), high sensitive electrochemical biosensors for detection of glucose and other electroactive biomolecules have been constructed.

Keywords: Plasmonics; Surface enhanced IR spectroscopy; Glucose; Plasmon enhanced electrochemistry

Reference
Chemotherapy is one of the major systemic treatments for cancer. In the current stage, cancer is primarily treated with small molecular anticancer drugs or nanotherapeutics consisting of anticancer drugs and nanocarriers. Unfortunately, these two drug delivery approaches exhibit several disadvantages. Therefore, a new drug delivery approach integrating advantages of free drugs and nanotherapeutics and avoiding their side-effects has become very attractive. Recently, we put forward a new concept, small molecule based nanodrug, for cancer therapy.\textsuperscript{1-5} To illustrate this concept, an amphiphilic drug-drug conjugate (ADDC) was constructed for small molecule based nanodrug. In details, a hydrophilic anticancer drug and a hydrophobic drug are linked together via a hydrolyzable ester bond. Ascribing to the amphiphilic property, the ADDC self-assembles into nanoparticles, leading to a longer blood circulation time than the free drugs, which facilitates the accumulation of anticancer drugs in tumor tissues via the EPR effect and the subsequent cellular internalization. Benefiting from the nano-characteristics of ADDC, the multidrug resistance (MDR) of tumor cells can be circumvented, resulting in high intracellular drug concentration. After hydrolysis of the ADDC, the two released free anticancer drugs exert synergetic cytotoxicity to the tumor cells, exhibiting higher apoptotic rate and anticancer activity than the individual free drugs. Furthermore, this concept has been successfully expanded into other small molecule based nanodrugs.

**Keywords:** drug delivery, nanodrug, small molecule, self-assembly

**Reference**


![Fig. 1 Self-assembly of amphiphilic small molecule prodrug.](image-url)
Active diffusion of Au nanoparticles on the upper surface of swarming bacteria

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In the study of swarming bacteria on solid surfaces, large-scale collective behavior of bacteria has been considered as a result of simple physical interactions, such as short-range collisions and long-range hydrodynamic interactions, with the fluid medium. However, physicists found that this kind of coordinated complex flow field could not be fully explained by mechanical views. To explore the dynamics of the collective behavior of bacteria especially on their upper surface, people have been using passive tracers such as micron-sized particles. Due to their size and inertia, however, the microparticles could not be separated from the biofilm and are more likely to collide with bacteria and thus getting entangled with their local movements. In this work, we use a new method to characterize the complex hydrodynamic flow field generated by swarming bacteria on a solid surface by using single plasmonic gold nanorods as the tracer. With a highly sensitive plasmonic imaging microscope, the movements of multiple single gold nanorods could be tracked in situ in real time. It was observed that the bright and light-weight nanotracers diffuse actively on the upper surface and had no direct contacts with the bacteria layer. By analyzing their individual trajectories, it was found that most of the nanorods undergo non-random directed motions that were apparently uncorrelated to the movements of the nearby bacteria. Such seemingly independent movements of the passive nanotracers can only be attributed to the complex flow field resulting from the collective behaviors of the underneath bacteria. When the activity of the bacteria were significantly reduced, the active diffusion of the nanorods also much reduced and their motion returned to normal diffusion.

Keywords: swarming bacteria, active diffusion, gold nanorod, single particle, darkfield microscopy
Development of In vivo Analytical Methods for Understanding the Processes of Oxidative Stress

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Reactive oxygen species have gained increasing attention in a wide range of brain research fields, because they are considered as the mediators of biochemistry of cellular pathology and are involved in oxidative stress and progressive neurodegenerative diseases. Our group is focusing on development of new methods for in vivo analysis of reactive oxygen species and related molecules, aiming at understanding the processes of oxidative stress, with high selectivity, sensitivity, and accuracy by creating a series of novel ratiometric sensors through integration of highly specific recognition and inner reference element [1-4].

In vivo analysis of chemical signals in brain extracellular fluid (ECF) using implanted electrochemical biosensors is a vital way to study brain functions and brain activity mapping. By implanting a microelectrode in a specific brain region, changes in the concentration of a variety of ECF chemical species can be monitored through applying a suitable electrical signal and usually recording the resulting Faradaic current. Our groups developed a novel methodology for designing electrochemical biosensors for simultaneous determination of two molecules via one recognition molecule. A new recognition molecule, Hemin-aminoferrocene, was firstly designed and synthesized to simultaneously detect pH and O2 in brain upon ischemia and in tumor during cancer starvation therapy, in which hemin was taken as recognition for O2 and pH through monitoring both current and potential outputs, Fc group was served as an inner reference. Followed by this dual signal outputs model, we further realized the simultaneous detection of pH and glucose in diabetic rat brain using glucose oxidase as specific recognition element for both glucose and pH in rat brain followed by ischemia [4].

Keywords: Reactive oxygen species; oxidative stress; in vivo; analytical methods

References
ECC Sequencing: Highly Accurate DNA Sequencing with Information Theory-based Error Correction

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Eliminating errors in next-generation DNA sequencing has proved challenging. Here we demonstrate error-correction code (ECC) sequencing, a method to greatly improve sequencing accuracy by combining fluorogenic sequencing-by-synthesis (SBS) with an information theory–based error-correction algorithm. ECC embeds redundancy in sequencing reads by creating three orthogonal degenerate sequences, generated by alternate dual-base reactions. The ECC sequencing approach allows a mixture of two types of nucleotide substrates to be introduced into each reaction cycle. The synthetic strands expose free 3’-OH groups that can be continuously extended until no nucleotides in the mixture can be further incorporated. Although each of such reactions provides only one degenerate sequence with partially defined base composition, one DNA template can be sequenced three times with three orthogonal combinations of dual-base mixes to provide three degenerate sequences, from which an unambiguous sequence can be accurately deduced. Sequencing errors in any degenerate sequence can be further identified and corrected in this approach. The ECC sequencing approach provides higher confidence of the sequence accuracy through the extra information received in the orthogonal flowgrams. We have built a laboratory prototype DNA sequencer to demonstrate the complete ECC process using fluorogenic SBS chemistry, and obtained single-end reads up to 250 bp with the first 200 bp free of error. ECC approaches should enable accurate identification of extremely rare genomic variations in various applications in biology and medicine.

Keywords: Next generation sequencing, Error correction code, Information theory, Fluoregenic

Reference
Functional DNA Sensors and Imaging Agents for Metabolomics

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While much progress has been made in genomics and proteomics, metabolomics has lagged behind, because it is much more difficult to detect metabolites such as metal ions and organic molecules sensitively and selectively in cells and living animals, because these metabolites are large in numbers, subtle in structural differences and trace in quantities. Most processes are based on a trial and error basis where successes in designing agents for one target can be difficult to translate success in designing agents for other targets. To meet these challenges, we have been able to use in vitro selection or SELEX to obtain DNAzymes, a new class of metalloenzymes that use DNA molecules exclusively for catalysis, and aptamers, a new class of nucleic acids that rivals antibodies, that can bind targets of choice strongly and specifically, and use negative selection strategy to improve the selectivity. By labeling the resulting DNAzymes and aptamers with fluorophore/quencher, gold nanoparticles, gadolinium, quantum dots or supermagnetic iron oxide nanoparticles, we have developed new classes of fluorescent, colorimetric and MRI agents for metal ions and a wide range of other targets with high sensitivity (down to 14 pM) and selectivity (> 1-million-fold selectivity).\textsuperscript{1}

While we and other have demonstrated much success in detecting metal ions and organic molecules in the environment using DNAzymes and aptamers, it is much more difficult to image these metabolites in living cells and animals, because delivery of these sensors/imaging agents into cells and animals and precise control of these sensors/imaging agents with high spatial and temporal resolution and minimal damage or perturbation to the biological systems quite challenging. To meet address these issues, we have conjugated DNAzymes/aptamers with gold nanoparticles, nanoshells and upconversion nanoparticles, and able to not only deliver the DNAzymes into cells and animals, but also achieve optical controls of DNAzyme sensors/imaging agents of metabolites using near IR light with high spatial and temporal resolution, with amplification methods that allow imaging endogenous metabolites such as Na\textsuperscript{+} (Fig. 1) in both living cells and animals.\textsuperscript{2}

Keywords: keyword 1, DNAzyme 2, Aptamers 3 fluorescent sensors 4 metabolites 5 metal sensors

Reference


Giant Magnetic Field Generated by Localized Plasmon

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A metallic nanocavity can act like an optical focusing lens to generate spatially highly confined plasmon with intense field of broad energy distribution. With such a localized nanocavity plasmon (NCP) we were able to obtain Raman images of a single molecule with sub-nm resolution and to induce nonlinear electron scattering process [1]. A new theory that correctly describes the interaction between the molecules and the NCP has been developed [2]. We recently also found that the gradient of the NCP could produce a giant magnetic field in situ, which allows breaking down the strict spin selection rule in optical spectroscopies [3].

References:
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Nanopore provides a confined space for single molecule analysis

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Protein nanopore exhibits nano-scale size and widely exists in nature. Aerolysin is one of the key member of protein nanopore that provides a confined space for effective electrochemical control of a single molecule interacting with the pore. Here, we establish aerolysin-based platform¹ for analyzing various small molecules such as oligonucleotides²-⁴, DNA methylation⁵ and peptides⁶, showing the excellent temporal and spatial resolution of aerolysin nanopore. To further improve the selectivity and sensitivity, the site-directed mutagenesis inside the protein is utilized to modify the specific group at single molecule interface⁷. This single molecule interface likes a “tuba”. As each molecule brings a characteristic movement, the “button” alone the “tuba” can be manipulated to organize beautiful notes for a single molecule music.

Keywords: nanopore, aerolysin, confined space, single molecule interface

Reference

Engineering of photo-responsive nanoplatforms for controlled drug release in cancer therapy

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In this talk, we will highlight our recent progress in the development of photo-responsive nanoplatforms for combating multidrug-resistant cancer. Firstly, magnetic nanoclusters with a tri-polymer coating was designed as a new class of reactive oxygen species (ROS)-responsive delivery vehicle for photodynamic therapy (PDT) with on-demand drug release regulated by light irradiation. As compared with free rose bengal (RB), the developed nanocarrier suggests a superior cytotoxicity owing to its efficient cellular uptake and improved intracellular trafficking mediated by ROS generation with light exposure. Controlled release of the host molecules (i.e. RB) or guest molecules (i.e. paclitaxel) from the bPEI-based nanoplatform could also be achieved through a photooxidation action sensitized by RB that occurs simultaneously during the photodynamic process. This approach promises specific payload release and highly effective PDT or PDT combined therapy in various cancer cell lines including breast (MCF-7 and multidrug resistant MCF-7 subline), SKOV-3 ovarian and Tramp-C1 prostate. Secondly, a novel delivery system was also designed by cross-linking of serum albumin on the surface of gold nanorods to achieve high drug loading efficiency. The as-prepared core-shell nanostructures exhibit excellent compatibility in various biological environments, tremendous doxorubicin loading capacity and greater photoacoustic signal generation efficiency than pristine gold nanorods. It performs a strong contrast enhancement for photoacoustic imaging of tumors. The therapeutic efficacy of drug-loaded nanocarriers against Tramp-C1 prostate cancer was further improved both in vitro and in vivo when subjected to additional near-infrared photothermal heating. Our finding suggests this developed core-shell nanoplatform is highly promising for in vivo theranostic applications. Additionally, the resulting drug nanocarrier was also designed for effective macrophage-mediated delivery to demonstrate how nanoparticle-loaded macrophages improve chemodrug distribution and retention ability to achieve enhanced antitumor effects. The serum albumin shell of these nanoagents served as a drug reservoir to delay the intracellular drug release and drug-related toxicity that impairs the host cell carriers. Near-infrared laser irradiation enabled on-demand payload release to destroy neighboring tumor cells. In comparison with pristine nanoparticles or free drug, the nanoengineered macrophages effectively demonstrate the importance and effect of homogeneous drug distribution and retention ability in cancer therapy.
Ionic liquid based method for deep coverage proteome analysis

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To achieve the deep-coverage proteome analysis, we proposed an ionic liquid based FASP protocol (i-FASP), by which with 1-dodecyl-3-methylimidazolium chloride (C12Im-Cl), both soluble and insoluble proteins could be efficiently extracted from cells, and denatured simultaneously at 95°C with DTT added, followed by on-filter alkylation, digestion and desalting. Different from the typical FASP protocol, most C12Im-Cl could be easily removed by ammonium bicarbonate. Contributed by the stronger extraction and solubilization efficiency of C12Im-Cl than SDS, and the higher biocompatibility with tryptic digestion, the identified protein and membrane protein number in HeLa cells was obviously improved within reduced time. Furthermore, such a protocol was successfully applied in the label-free based quantitation of human liver tissues, and showed superiority to traditional FASP method.
Biomedical Properties of Nanoparticles: Safety and Medicine

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In the talk, we will discuss analytical approaches for quantifying and imaging nanomaterial interactions with different biological levels like cell, tissues and living body, in order to understand the nanosafety issue, medical applications of nanomaterials, etc. To this end, the rational characterization and quantitative analysis of nanomaterials when interacting with biological systems is one of the most difficult bottlenecks, the conventional approaches developed for biomedical sciences are mostly not adequate for the need of the proper analyses of nanomaterials when in such complex systems as cells and living body. To be concise and concentrative, we will mostly focus on the scientific approaches for analyses of nanomaterials interactions in biomedical applications, including the quantification approaches of nanomaterials in biological systems, the characterization of nano/bio weak-interactions which play key roles in determining biomedical behaviors (function or toxicity) of nanomaterials in vivo, such as the protein-nanosurface interaction, etc. We will also show how to apply the principle of these analytical approaches to identify biomarkers for some human diseases, which leads to cancer therapeutics of novel concept cancer nanotechnology.

Figure 1, The bio-effects of interface interaction of proteins with nanosurface are applied to the enrichment of serum biomarkers and human diseases detections.

Keywords: Nanomaterials, Nanoparticles, Biomedical effects, Cancer therapy & diagnosis, Nanosafety.

Reference

Sensing of Biorelevant Species by Simple Receptors in Aggregate Forms

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We have recently explored a strategy for highly sensitive and selective sensing of biologically relevant species by using simple receptors which would otherwise not have been able to do those if not existing in their aggregate forms. This is inspired by the specific recognition of substrates by enzymes of high affinity, despite the weak and nonselective interactions. In the substrate-enzyme interactions it was noted that the binding receptors are well organized when the substrate is present. We therefore initiated our project by designing simple receptors that may not be that optimal when existing in their monomeric forms yet highly capable when turning into their aggregate forms for biologically relevant species that in general bear multiple binding groups, as those in the enzymatic interactions. We have succeeded in developing sensing systems for saccharides, ATP, and NAD(H). The receptors can be simple building blocks contacting binding sites such as phenyl boronic acid or aldehyde groups, or mixtures of them or those formed in situ via reversible dynamic reactions.

I thank the supports of the NSF of China and the Ministry of Education of China. I also thank the creative efforts of my students in the research group.
Molecular Interactions between Two-Dimensional Materials and Biological Molecules

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Two dimensional mono-layered materials such as graphene and transition metal dichalcogenides (TMDs) like MoS$_2$, WS$_2$ have been extensively investigated for potential applications in advanced microelectronics such as organic solar cells, light emission diodes, as well as biosensors. For biosensing applications, it is necessary to understand the molecular interactions between 2D materials and biological molecules such as peptides and proteins in situ in detail. Unfortunately it is very difficult to probe such interactions due to the lack of appropriate tools. In the recent years, we demonstrated that sum frequency generation (SFG) vibrational spectroscopy, a nonlinear optical spectroscopic technique, is a powerful tool to elucidate molecular interactions between 2D materials and biological molecules at the solid/liquid interface in situ in real time. We found that the aromatic amino acids strongly interact with graphene, which determine whether a peptide or protein can stand up or lie down on the graphene surface. By carefully designing the sequence of a peptide or mutating key amino acids in a protein, it is feasible to optimize the interactions between graphene and biological molecules so that the biomolecules can adopt a desired orientation. We also studied molecular interactions between peptides or proteins and transition metal dichalcogenides (TMDs) like MoS$_2$, WS$_2$. The biological molecules interact with the TMDs very differently from graphene. Aromatic amino acids do not interact more favorable with TMDs compared to other amino acids. No disulfide bonds were found between cysteine and MoS$_2$ or WS$_2$ monolayer. Instead, the hydrophobic interaction determines whether a protein is denatured or not on a TMD surface. We believe that this is the first time to elucidate detailed interaction mechanisms between biological molecules and 2D mono-layered materials.

Keywords: Graphene, Transition Metal Dichalcogenides, Peptides, Proteins
Molecularly imprinted nanoparticles: Can they be a new access to cancer targeted therapy and immunotherapy?

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Abstract
Cancer targeted therapy and immunotherapy are two promising methodologies for cancer treatment, for which antibodies are the workhorses for cancer targeting. However, antibodies are associated with apparent disadvantages. They are hard to prepare and thereby expensive. Besides, they are often associated with inefficient specificity and poor stability. Therefore, alternatives of antibodies that can overcome these disadvantages are of significant importance. Molecular imprinting is an important technology for creating affinity materials with antibody-like binding properties. Molecularly imprinted polymers (MIPs) are prepared through polymerization in the presence of template molecules. As compared with antibodies, MIPs are easier to prepare, much more cost-efficient and stable. In recent years, we have developed several general and facile molecular imprinting approaches for the preparation of MIPs specific to glycoproteins, glycans and monosaccharides. The prepared MIPs exhibited highly desirable binding properties, including high affinity, high specificity and resistance to interference. These features made the MIPs appealing alternatives of antibodies for many important applications. Applications in affinity separation, proteomic analysis, disease diagnosis, cancer cell/tissue imaging, single cell analysis and cancer targeted photothermal therapy have been demonstrated. Particularly, molecularly imprinted nanoparticles (MINPs) with monosaccharides such as sialic acid and mannose as the templates have shown cancer cell targeting capability and thereby great potentials as targeting reagents for promising applications. More recently, we further explore the possibilities using glycan-imprinted nanoparticles for cancer targeted therapy and immunotherapy. In this talk, we will introduce related background and discuss recent preliminary results. We will also briefly sketch remaining challenges and directions for future development.

Representative publications:
Sensitized upconversion nanoparticles for biological applications

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Lanthanide-doped upconversion nanoparticles (UCNPs), which can sequentially absorb two or more near infrared (NIR) photons and emit one photon with higher energy, have been widely applied in biological areas, such as bio-sensing, nanothermometry, drug delivery, and photodynamic therapy.\(^1,2\) The NIR-excitation property confers them distinct advantages such as effectively eliminated autofluorescence, increased penetration depth and reduced photo-damage. However, further applications have been constrained by the low upconversion efficiency, which has become one of the center problems in this field.\(^3,4\)

Sensitization by NIR fluorophores with strong absorption in NIR is an effective strategy to enhance the upconversion luminescence, which could enhance fluorescence by thousands of times. Since proposed in 2012, this strategy has been optimized by many scientists.\(^5,6\) However, most of relevant works were conducted in organic solvents. Applications in biological samples are still rare,\(^7,8\) and there is no systematic study of sensitization in aqueous solution. We have systematically studied the sensitization in water, which paves the way for its bioapplications. Furthermore, we constructed nanoprobes for biological assay based on sensitized UCNPs. We used small molecule dyes as the switch to trigger the sensitization of the luminescence efficiency of UCNPs by the reaction with targets and spontaneously realize the high signal-to-background ratio responses.

**Keywords:** Lanthanide-doped upconversion nanoparticles, sensitization, biological assay

**References**

Self-powered systems for medical sciences and bioengineering

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Self-powered system is a system that can sustainably operate without an external power supply for sensing, detection, data processing and data transmission. Nanogenerators (NG) were first developed for self-powered systems based on piezoelectric effect and triboelectrification effect for converting tiny mechanical energy into electricity, which have applications in internet of things, environmental/infrastructural monitoring, medical science, environmental science and security. NGs have three major application fields: micro/nano-power source, self-powered sensors and blue energy. We will present the applications of the NGs for harvesting body motion energy that will be used for medical science and bioengineering.

Reference

About speaker:
Dr. Zhong Lin (ZL) Wang is the Hightower Chair in Materials Science and Engineering and Regents' Professor at Georgia Tech, and Founding Director and Chief Scientist at Beijing Institute of Nanoenergy and Nanosystems, Chinese Academy of Sciences. Dr. Wang has made original and innovative contributions to the synthesis, discovery, characterization and understanding of fundamental physical properties of oxide nanobelts and nanowires, as well as applications of nanowires in energy sciences, electronics, optoelectronics and biological science. His discovery and breakthroughs in developing nanogenerators establish the principle and technological road map for harvesting mechanical energy from environment and biological systems for powering a personal electronics. His research on self-powered nanosystems has inspired the worldwide effort in academia and industry for studying energy for micro-nano-systems, which is now a distinct disciplinary in energy research and future sensor networks. He coined and pioneered the field of piezotronics and piezo-phototronics by introducing
piezoelectric potential gated charge transport process in fabricating new electronic and optoelectronic devices. This breakthrough by redesign CMOS transistor has important applications in smart MEMS/NEMS, nanorobotics, human-electronics interface and sensors. Dr. Wang was elected as a foreign member of the Chinese Academy of Sciences in 2009, member of European Academy of Sciences in 2002, fellow of American Physical Society in 2005, fellow of AAAS in 2006, fellow of Materials Research Society in 2008, fellow of Microscopy Society of America in 2010, fellow of Royal Society of Chemistry, and fellow of the World Innovation Foundation in 2002. He received 2016 Distinguished Scientist Award from (US) Southeastern Universities Research Association, 2015 Thomas Routers Citation Laureate award, 2014 World Technology Prize in Materials; 2014 the James C. McGroddy Prize for New Materials from America Physical Society, 2013 ACS Nano Lectureship award, 2012 Edward Orton Memorial Lecture Award and 2009 Purdy Award from American Ceramic Society, 2011 MRS Medal from the Materials Research Society, 1999 Burton Medal from Microscopy Society of America. He has authored and co-authored 6 scientific reference and textbooks and over 1300 peer reviewed journal articles (16 in Nature and Science, 25 in Nature and Science sister journals), edited and co-edited 14 volumes of books on nanotechnology, and held over 100 US and foreign patents. From SCI data base, his entire publications have been cited for over 130,000 times with an h-index of 177 [http://www.researcherid.com/rid/E-2176-2011]; Google scholar gives a citation of 173,000 with an h-index of 204 [http://scholar.google.com/citations?user=HeHFFW8AAAAJ&hl=en]. He has delivered over 900 planary, keynote, invited and seminar talks at international and national conferences as well as universities and research institutes worldwide. Details can be found at: http://www.nanoscience.gatech.edu
From plasmon-enhanced Raman spectroscopy to plasmon-mediated chemical reaction

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The excitation of surface plasmons (SPs), collective oscillation of conduction electrons in nanostructures, can significantly redistribute photon, electron and heat energy in time and space. In the past three decades, we have developed plasmon-enhanced Raman spectroscopy (PERS) including SERS/TERS/SHINERS with ultra-high sensitivity. As shown in Figure 1, there are two distinct trends: i) the fundamental research on the methodologic development for pushing the limit of PERS to single-molecule sensitivity, sub-nanometer spatial resolution and femto-second temporal resolution, etc.; ii) the practical application of being developed to a versatile analytical tool for surface, material, life, environmental, forensic and food sciences, and then further to the widely used commercial instruments.

![Figure 1](image)

Figure 1 Two different approaches of PERS.

Recently we have extended PERS\(^1\)\(^-\)\(^3\) to another important branch of nanoplasmonics: plasmon-mediated chemical reactions (PMCR), which exhibit differences from, and potential advantages over traditional photo-chemistry and thermal-chemistry. We have tried to use the confined thermal field with sharp gradient and hot carriers in the PMCR systems to drive chemical reactions with unique characteristics.

**References**

Transition metal ions play vital roles in cellular metabolism, gene expression, apoptosis, neurotransmission, and so forth. It is also associated with physical growth retardation and neurological disorders such as cerebral ischemia and Alzheimer's disease. Platinum-based antitumor drugs play an important role in the treatment of various malignancies such as colorectal and testicular cancers. In this context, our lab has been focusing on the following two research subjects: 1) molecular sensing and imaging of bio-medicinal inorganic species; 2) design and delivery of platinum-based antitumor complexes. In this lecture, I will summarize our recent works in these two topics, and illustrate the close links between the molecular design of these compounds and their bioanalytical and bio-medical applications.

In the search for novel sensors of bio-metals and inorganic signalling species, we have been concentrating on the design of fluorescent probes that can be excited by visible light and have ratiometric potential. The targeting properties to specific sub-cellular compartments such mitochondria or lysosomes are also desirable. On the other hand, the biological and pharmacological properties of metallodrugs can be finely tuned by rationale design of the coordination sphere of metal centres, or by conjugating the drug molecules with additional targeting vehicles.

Keywords: zinc sensors, platinum drugs, delivery

Reference