The 4th International Conference on Nucleic Acid-Protein Chemistry and Structural Biology for Drug Discovery

2014 第四届国际核酸与蛋白质化学及结构生物学药物研究大会

Sichuan University (四川大学)

Co-Chairs: Zhen Huang (黄震), Xiao-Qi Yu (余孝其), Zhi-Xiong Xiao (肖智雄)

Organizers: Sichuan University College of Life Sciences (四川大学生命科学学院),
College of Chemistry (四川大学化学学院), The State Key Laboratory of Biotherapy and Cancer Center (四川大学生物治疗国家重点实验室),
Selenium Nucleic Acid Research Institute (SeNA), Georgia State University

Place: 四川大学生物治疗国家重点实验室/生物治疗协同创新中心

Time: June 3-6, 2014 (The registration starts at 8:00 am on June 3, 2014)
Science is Art.
Sichuan University (四川大学)

Place: The State Key Laboratory of Biotherapy and Cancer Center

Time: June 3-6, 2014

Co-Chairs: Zhen Huang (黄震), Xiao-Qi Yu (余孝其), Zhi-Xiong Xiao (肖智雄)

Committee Members:
Yuquan Wei (魏于全), Zhi-Xiong Xiao (肖智雄), Xiao-Qi Yu (余孝其), Yuanwei Chen (陈元伟), Zhen Xi (席真), Xiang Zhou (周翔), Xiaogang Qu (曲晓刚), Luoting Yu (余洛汀), and Zhen Huang (黄震)。

Contents

Program ................................................................................................................. 4
Abstracts ................................................................................................................ 6
Sponsors .................................................................................................................. 46
# Conference Agenda

## Tuesday, June 3, 2014

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:00 – 21:00</td>
<td>Registration at the Hotel, Check-in, and Visit to Sichuan University Campuses (in the morning), and Bio-Tech/Hi-Tech Park (in the afternoon), Reception (starting at 17:00 in Angel Hotel, 成都天使宾馆, the lobby area), Speakers’ Dinner, and Social Hours.</td>
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## Wednesday, June 4, 2014

**Chair:** Zhen Huang

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
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<tbody>
<tr>
<td>8:30 – 8:45</td>
<td>Welcome &amp; Opening Speech: <strong>Yu-Quan Wei</strong> (Vice President of Sichuan University)</td>
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<tr>
<td>8:45 – 9:30</td>
<td>Keynote Speech: <strong>Steven A. Benner</strong> “Diagnostic, Medicine, and New Life Forms from Artificial DNA”</td>
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<tr>
<td>9:30 – 10:00</td>
<td><strong>Zhi-Xiong Xiao</strong> “The oncogenic activity of MDMx is associated with physical interaction and suppression of retinoblastoma protein”</td>
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<tr>
<td>10:00 – 10:30</td>
<td><strong>Zhen Xi</strong> “QSAR on Biomolecular Interactions”</td>
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<td>10:30 – 11:00</td>
<td>Speaker Group Photo and Coffee/Tea Break <em>Chair: Xiao-Qi Yu</em></td>
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<tr>
<td>11:00 – 11:30</td>
<td><strong>Xiaogang Qu</strong> “Chemical Controlled Biomolecular Recognitions and Their Applications in Disease Diagnosis and Treatment”</td>
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<tr>
<td>11:30 – 12:00</td>
<td><strong>Zhen Huang</strong> “Selenium Nucleic Acids (SeNA) for Chemical and Structural Biology of Nucleic Acid-protein Complexes”</td>
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<tr>
<td>12:00 – 13:30</td>
<td>Lunch <em>Chair: Zhi-Xiong Xiao</em></td>
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<tr>
<td>13:30 – 14:00</td>
<td><strong>Xiang Zhou</strong> “Chemical epigenetics of nucleic acids”</td>
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<tr>
<td>14:00 – 14:30</td>
<td><strong>Zhenjun Yang</strong> “Biological Properties of Isonucleotide (IsoNA) Modified siRNAs”</td>
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<td>14:30 – 15:00</td>
<td><strong>Xiao-Qi Yu</strong> “Macrocyclic Polyamine-Based Non-Viral Gene Vectors”</td>
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<tr>
<td>15:00 – 15:30</td>
<td><strong>Xiangyang Fang</strong> “Structural Studies of Large RNAs using Small Angle X-ray Scattering (SAXS)”</td>
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<td>Time</td>
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<tr>
<td>15:30 – 16:00</td>
<td>Coffee/Tea Break</td>
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**Thursday, June 5, 2014**

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<tr>
<th>Time</th>
<th>Session</th>
<th>Speaker</th>
<th>Title</th>
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<tbody>
<tr>
<td>8:30 – 9:00</td>
<td></td>
<td>Jia Sheng</td>
<td>“Crystal Structure Studies of 2'-5'-Linked RNA”</td>
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<tr>
<td>9:00 – 9:30</td>
<td></td>
<td>Zhuo Tang</td>
<td>“DNA Display for Drug Discovery”</td>
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<tr>
<td>9:30 – 10:00</td>
<td></td>
<td>Yamei Yu</td>
<td>“Crystal structure of integrin α4β7 complexed with Fab and small molecular drug”</td>
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<tr>
<td>10:00 – 10:30</td>
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<td>Qiang Chen</td>
<td>“Structural View of Netrin Receptors in Axon Guidance”</td>
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<td>10:30 – 11:00</td>
<td>Coffee/Tea Break</td>
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<td>Chair: Yuanwei Chen</td>
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<tr>
<td>11:00 – 11:30</td>
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<td>Jianhua Gan</td>
<td>“Structural insight into the mechanism of RNase III Action”</td>
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<tr>
<td>11:30 – 12:00</td>
<td></td>
<td>Ganggang Wang</td>
<td>“Structural Insight Into the Interaction between Replicative Helicase and Primase”</td>
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<tr>
<td>12:00 – 12:30</td>
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<td>Wen Zhang</td>
<td>“Facilitation of Nucleic Acid X-ray Structure Determination by Selenium Functionalization”</td>
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<tr>
<td>12:30 – 13:30</td>
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<td>Lunch</td>
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<tr>
<td>13:30 – 21:00</td>
<td></td>
<td>Trip to LeShan</td>
<td>Return to Chengdu on Friday (4 pm, on June 6). Drs. Benner and Huang will give lectures at LeShan Normal College in the morning on Friday.</td>
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**Drs. Benner and Huang will give lectures at LeShan Normal College in the morning on Friday.**
Diagnostic, Medicine, and New Life Forms from Artificial DNA

Steven A. Benner*, Foundation for Applied Molecular Evolution, and The Westheimer Institute for Science and Technology, Gainesville, Florida USA; email: sbenner-(at)-ffame.org

Watson-Crick base pairing in DNA and RNA (collectively xNA) follows two rules of complementarity: (a) size complementarity, where large purines (A and G) pair with small pyrimidines (T or U, and C), and (b) hydrogen bonding complementarity, where hydrogen bond donors pair with hydrogen bond acceptors on its complement. These features, as well as the repeating charge and the limited flexibility of their sugar-phosphate backbones, allow xNA molecules to direct their own replication. However, xNA molecules can also fold in solution, where selected xNA molecules can act as receptors, ligands, and even catalysts for chemical reactions, much like proteins.

The Foundation for Applied Molecular Evolution and its corporate partner, Firebird Biomolecular Sciences LLC, have developed several alternative forms of xNA where the nucleobases and hydrogen bonding patterns have been rearranged, supplemented, and modified. This talk will describe those "nonstandard" nucleic acids how they are being applied in human diagnostics and medicine. These include:

(a) Artificially expanded genetic information systems (AEGIS). In AEGIS xNA, the hydrogen bond donor and acceptor groups of the bases are rearranged to increase the number of replicable building blocks from four to six. We will show how tools exploiting AEGIS nucleotides can cleanly diagnose the presence of infectious agents, including the viruses that cause Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), and HIV.

(b) Self-avoiding molecular recognition systems (SAMRS). In SAMRS, hydrogen bonding units are strategically altered or removed to create nucleotide analogs (A*, T*, G*, and C*), where SAMRS A* binds to natural T, SAMRS *G binds to natural C, SAMRS C* binds to natural G, and SAMRS T* binds to natural A, but SAMRS A* does not bind to SAMRS T*, and SAMRS G* does not bind to SAMRS C*. This means that SAMRS primers and probes can be added to an assay mixture in any numbers and any amounts without their interacting with each other to create artifacts. This allows essentially unlimited multiplexing in xNA-targeted assays, creating low per-assay cost. We will show an example where an AEGIS-SAMRS combination allows simultaneous detection of over 20 RNA viruses carried by common mosquitoes.

(c) Technology to allow AEGIS xNA molecules to evolve and adapt to meet specific functions. In collaboration with Prof. Zhen Huang, Weihong Tan, and Joseph Piccirilli, we have used in vitro evolution to create DNA aptamers that bind to breast cancer cells and liver cancer cells, often with high selectivity. These have potential not only to diagnose cancer early in the progression of the disease, but to also serve as therapeutic and drug-targeting agents.

Selected Publications:
Steven A. Benner

Prof. Steven A. Benner (Ph.D.) received his B.S. and M.S. degrees in Molecular Biophysics and Biochemistry in 1976 from Yale University. He received his Ph.D. in Chemistry in 1979 from Harvard University under the supervision of Professor Frank H. Westheimer and Prof. Robert B. Woodward. After three years as a Xerox Fellow and a Junior Fellow in the Harvard Society of Fellows, he became an Assistant Professor of Chemistry at Harvard in 1982. In 1985, he moved to the Swiss Federal Institute of Technology in Zürich, Switzerland, first as an Associate Professor, and then a professor of Organic Chemistry and Biomolecular Chemistry. In 1997, he moved to the University of Florida, where he became V. T. and Louise Jackson Distinguished Professor of Chemistry, before establishing the Foundation for Applied Molecular Evolution and The Westheimer Institute for Science and Technology, where he is now a Distinguished Fellow.

The Benner laboratory works to join two scientific communities, "natural historians" and "physical scientists". To this end, the laboratory helped pioneer synthetic biology. In 1984, the laboratory completed the first total synthesis of a gene encoding an enzyme, introducing "engineer-ability" features that are today routine throughout synthetic biology. The Benner laboratory was also the first to increase the number of building blocks in DNA. Benner’s synthetic DNA today support diagnostics products having sales of $100 million, helping to personalize care of 400,000 patients annually. Emerging synthetic genetics enable highly multiplexed detection of nucleic acids, DNA-targeted diagnostics at points of care, next-generation sequencing, and nanostructure assembly. The laboratory's "second generation" model for DNA is guiding the search for life on other planets.

The Benner laboratory also founded the field of experimental paleogenetics, which resurrects ancestral genes from extinct organisms for laboratory study. Paleogenetics brings experimental methods to bear on historical models in biology, has generated drug candidates for diabetes, cancer, and gout, and is helping us understand hypertension, alcoholism, and inflammation.

In informatics, the Benner laboratory was the first to exhaustively cross-compare modern sequence databases, provided the first compelling tools to predict protein folds from evolutionary analyses of protein sequences, and helped develop planetary biology and astrobiology, which connect biomolecular structure in terran life to the planet and the cosmos. This work generated the first commercial evolutionary organized database, the MasterCatalog.

In small molecule chemistry, Benner group holds the US patent in dynamic combinatorial chemistry; Nobel laureate Jean-Marie Lehn holds the European patent. Dynamic combinatorial chemistry uses evolutionary concepts to generate small molecule lead drug candidates.

Prof. Benner is also a serial entrepreneur. He founded Sulfonics and, later, EraGen Biosciences, which was recently acquired for $34 million. Alantos, founded on his technology, was acquired for $220 million. Firebird Biomolecular Sciences LLC is the third company to be based largely on his technology; Firebird today makes reagent innovations for diagnostics, biotechnology, and nanostructures available to the public.

Prof. Benner is also well known for his public outreach and science education. His latest book, entitled *Life, the Universe, and the Scientific Method*, describes how scientists develop new knowledge in fields that do not easily lend themselves to “hypothesis based research”. He is also in much demand as a public lecturer, speaking to audiences on the origin of life, the creation of artificial life, and the search for extraterrestrial life throughout the Solar System.
The oncogenic activity of MDMx is associated with physical interaction and suppression of retinoblastoma protein

Haibo Zhang, Yujun Zhang, Wei Qiu and Zhi-Xiong Xiao*

Center of Growth, Metabolism and Aging, College of Life Sciences, Sichuan University, Chengdu, China;
email: jimzx@scu.edu.cn

Inactivation of Rb plays a critical role in the development of human malignancies. We have previously shown that MDM2, an ubiquitin E3 ligase and a major negative regulator of p53, binds to and promotes proteasome-mediated degradation of Rb independent of p53. MDMX, a homolog of MDM2, also binds to and inhibits p53 transactivation activity, yet it does not possess an ubiquitin E3 ligase activity. In this study, we show that MDMX binds to and promotes proteasome-mediated degradation of Rb in a MDM2-dependent manner. The C-terminal Ring domain of MDMX binds to the Rb C-pocket and enhances MDM2-Rb interaction. Knockdown of MDMX induces Rb protein accumulation, cell cycle G1 arrest, and premature cellular senescence, which can be reverted by simultaneous knockdown of Rb. Furthermore, ablation of MDMX significantly suppresses tumor growth, concomitant with Rb accumulation, in an animal xenograft model. Together, these results demonstrate that MDMX possesses oncogenic activity associated with suppression of Rb and suggest that both MDM2 and MDMX can be targets for cancer therapy.

This work is supported by the 973 Program of China (2012CB910700) and National Natural Science Foundation of China (NSFC) grant (31171362).

Recent Publications:
Zhi-Xiong Xiao, PhD
National Distinguished Expert
Professor and Dean
College of Life Sciences
Sichuan University, Chengdu, China

Biography:
Education:
• BS (1981) Biochemistry, Sichuan University
• PhD (1991) Cell and Molecular Biology Program, University of Massachusetts at Amherst
• Postdoctoral training (1991-1995), Dana-Farber Cancer Institute, Harvard Medical school

Employment:
1996-2006: Assistant Professor, Associate professor, Departments of Biochemistry and Medicine, Boston University School of Medicine
2007-2019: Professor, Boston University School of Medicine
2010- present: Professor and Dean College of Life sciences, Sichuan University, Chengdu

Awards and Other Positions:
1991: Anna Fuller Foundation postdoctoral award
1994: American Cancer Society Senior postdoctoral award.
2009: 1st 1000-talent Scholar, (首批千人计划）
2010: 1st 100-talent scholar，Sichuan Province
2010: director: Center for growth, metabolism and aging, Sichuan University
2011: National distinguished expert
2011 Chief Scientist, National Research Program (973) on Cancer Metastasis, China

Research Interests:
Cell cycle, metastasis, signal transduction, cancer biology
My lab has been working on the function and regulation of p53 family and Rb in tumorigenesis.
Current focuses are the role of p63 in cell migration and cancer metastasis; validation of biological active peptides in regulation p53 and Rb; stem cells and cancer cell metabolism.
QSAR on Biomolecular Interactions

Zhen Xi
State Key Laboratory of Elemento-Organic Chemistry and Department of Chemical Biology, Collaborative Innovation Center of Chemical Science and Engineering, Nankai University, Tianjin 300071, China
zhenxi@nankai.edu.cn

Being able to quantitatively predict the risk of drug resistance and drug selectivity at molecular level will greatly benefit our understanding on biomolecular interactions, such as drug-protein interaction, substrate-enzyme interaction, signal effector-receptor interaction, protein-protein interaction (PPI) and protein-nucleic acid interaction, etc. Many efforts have been dedicated towards these issues.[1-9] Recently, a new method, called MB-QSAR (Mutation-dependent Biomacromolecular Quantitative Structure-Activity Relationship) was developed in our group[10-12], which extended Comparative Molecular Field Analysis (CoMFA)[13] and Comparative Molecular Similarity Indices Analysis (CoMSIA).[14]

In this talk, I will discuss our recent progress on MB-QSAR for biomolecular interactions. I will present several examples that MB-QSAR can give accurate prediction on drug resistance, drug selectivity and enzyme activity. My topics will cover 1) herbicide resistance of acetohydroxyacid synthase (AHAS) mutants against a series of inhibitors, and their quantitative structure-resistance relationship for AHAS mutants; 2) drug resistance of HIV-1 protease mutants against six approved drugs for AIDS (saquinavir, indinavir, ritonavir, nelfinavir, amprenavir and lopinavir), and their quantitative structure-resistance relationship; 3) drug selectivity on different kinases for some kinase inhibitor drugs, such as sunitinib, dasatinib, gefitinib, bosutinib and erlotinib, and their quantitative structure resistance/selectivity relationships in kinome. We will also discuss on the issue of prediction of enzyme activity, specifically the catalytic activity of PPO enzyme, which related to human Variegate Porphyria disease by its mutation.[15-17]

Based on these studies, we will discuss our proposal for a new molecular design technique--Targetome Structure Based Drug Design (TSBDD).

Acknowledgements
This work was financially supported by MOST (2010CB126103, 2011BAE06B05), NSFC (20932005, 21332004).

REFERENCES
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2001-Present Changjiang Scholar Professor, Nankai University
1994-2001 Research Fellow & Research Associate, Harvard Medical School
1994 PhD Uppsala University, Sweden
1988 MS Nankai University, China
1983 BS Central China Normal University

Research Interests:
1) Medicinal Chemistry of Nucleic Acid (siRNA),
2) Molecular Basis of Pesticide Action,
3) QSAR on Biomolecular Selectivity and Drug Resistance.

Selected Publications:
6. The minimum activation peptide from ilvH can activate the catalytic subunit of AHAS from different species, Y. Zhao, C. Niu, X. Wen, Z. Xi, ChemBioChem 2013, 14, 746-752.
Chemical Controlled Biomolecular Recognitions and Their Applications in Disease Diagnosis and Treatment

Meng Li, Li Wu, Wen Li, Peng Shi, Nan Gao, and Xiaogang Qu*

More and more evidences have shown that many biological important processes and disease pathogenesis are related to the conformation and assembly state of specific gene, involved proteins and enzymes. In this report, we summarize our recent research progress in this field [1-10]. This work was supported by 973 Project, and NSFC.

References
Xiaogang Qu

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2002 - Present  Professor of Chemistry, Changchun Institute of Applied Chemistry, Chinese Academy of Sciences
2006.12-2007.5  Visiting Professor, University of California at Santa Barbara with Nobel Laureate Prof. Alan J. Heeger
2000-2002  NSF Laboratory for Molecular Sciences, California Institute of Technology with Nobel Laureate Prof. A. H. Zewail
1996-2000  Department of Biochemistry, School of Medicine, UMC with Prof. J. B. Chaires
1989-1995  PhD Candidate, President’s Award of the Chinese Academy of Sciences (1995), Changchun Institute of Applied Chemistry, Chinese Academy of Sciences
Selenium Nucleic Acids (SeNA) for Chemical and Structural Biology of Nucleic Acid-protein Complexes

Rob Abdur, Wen Zhang, Jianhua Gan, Oksana O. Gerlits, Huiyan Sun, Jozef Salon, Julienne Caton-Williams, Sibo Jiang, Hehua Liu and Zhen Huang*, Department of Chemistry & Department of Biology, Georgia State University, Atlanta, Georgia, USA; email: Huang@gsu.edu

Nucleic acids play multiple and essential functions in cells and expand dramatically the complexity of life by serving as genetic information carrier, catalyst, and regulator. Nucleic acid nanotechnology and therapeutics exploration help better understand properties and behaviors of nucleic acids in vitro and in vivo. Nucleic acid chemical functionalization and structural study help understanding nucleic acids in cells and offer a great opportunity to therapeutic discovery. 3D structure studies of nucleic acids and their protein complexes provide novel insights into these bio-macromolecules. Crystallography is a powerful tool for structure determination of nucleic acids and protein-nucleic acid complexes with high resolution. However, crystallization and phase determination, two major bottleneck problems, have largely slowed down structural determination of nucleic acids and their protein complexes. Crystal structures of protein-nucleic acid complexes are commonly determined by selenium-derivatized proteins via MAD or SAD phasing. Herein we report the first protein-nucleic acid complex structure determined by selenium-derivatized nucleic acids. The RNase H/RNA/DNA complex is used as an example to demonstrate the proof of principle. Our high-resolution crystal structure indicates that this Se-replacement results in a local subtle unwinding on RNA/DNA substrate duplex, thereby shifting the RNA scissile phosphate closer to the transition state of the enzyme-catalyzed reaction. We also observed that the scissile phosphate forms a hydrogen bond with the water nucleophile and helps positioning the water molecule in the structure. Consistently, we have discovered that the substitution of a single oxygen atom with a selenium atom on a DNA-guiding sequence can largely accelerate RNase H catalysis. Our structural and catalytic studies shed new light on the guide-dependent RNA cleavage (Ref. 1). Furthermore, our laboratory has pioneered and developed atom-specific substitution of nucleic acid oxygen with selenium (Ref. 1-18) that can be used as an atomic probe for structure and function studies of nucleic acids. This work is supported by NIH (R01GM095881 and GM095086) and NSF (MCB-0824837 and CHE-0750235).

Selected Publications:
Zhen Huang

Prof. Zhen Huang (Ph.D.) was born in 1964 and raised in Sichuan, China. He received his B.S. degree from Sichuan University in 1984 (under the supervision of Professor Shulin Chen), M.S. from Peking University in 1987 (under the supervision of Professor Wen Zhong), and Ph.D. degree from Swiss Federal Institute of Technology (ETH, Zurich) in 1994 (under the supervision of Professor Steven Benner). In 1994, he joined the Department of Genetics at Harvard Medical School as a research fellow, in Laboratory of Professor Jack Szostak (Nobel Laureate in Medicine in 2009). He was hired in 1998 by Brooklyn College, City University of New York, as assistant professor and was later promoted to associate professor with tenure. In 2004, Dr. Huang was recruited to Chemistry Department, Georgia State University, is Professor of Chemistry and Chemical Biology, and is also University Distinguished Professor Awardee of Georgia State University. He has received several awards, including Georgia Distinguished Cancer Scientists Award, from The State of Georgia (GCC). He is also very active in community services; he has served as editors and guest editors for several journals and books, and is the first President of Chinese-American Chemistry & Chemical Biology Professors Association (CAPA; also one of the three Co-Founders). He has pioneered and developed selenium and tellurium derivatizations of nucleic acids for structure and function studies of nucleic acids, protein-nucleic acid complexes, and nucleic acid-small molecular ligands (such as anticancer drugs). His current research interests are in selenium and tellurium derivatizations of DNAs and RNAs for X-ray crystallographic studies of nucleic acids and protein complexes (especially for Cancer Research), synthesis of analogs of nucleosides and nucleotides for structure, function and anticancer studies, development of RNA microchip technology for direct detection and quantitation of gene expression profile for Cancer Early Detection, nanomaterial-assisted novel RNA microchip, modified nucleic acid-based nano-medicine, nucleic acid-based cancer diagnosis, in vitro selection, evolution and characterization of ligand-binding and catalytic RNAs and DNAs. His research has been funded by federal agencies, including NIH, NSF, DOD and CDC, state funding agencies, the distinguished cancer scholar award, and private fundings (such as industries). He has received many US and European patents, and many US and international patents are pending.
Chemical epigenetics of nucleic acids
Tiantian, Shaoru Wang, Tianlu Wang, Tingting Hong, Pu Guo, Xiang Zhou*

Molecular Sciences, Wuhan University, Hubei, Wuhan 430072, P. R. of China;
email: xzhou@whu.edu.cn

Heredity and variation are universal in the biological world. Phenotypes and genetic information are not only determined by genetic constitution but also can be altered and transferred through modification of genes and proteins, through processes referred to as epigenetics. DNA methylation is one of the most significant epigenetic events which greatly influence gene activation, gene imprinting, chromatin stability, and so on. The level of methylation in genome and certain regions should be in a normal range. We shall report our recent findings about chemical epigenetics of nucleic acids.

These works are supported by the National Natural Science Foundation of China (90813031, 30973605, 21072155 & 20802055), National Key Foundation for Infectious Diseases (Protection and treatment of AIDS, virus hepatitis, 2008ZX10003-005), Open funding of the State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, the Chinese Academy of Sciences, the Fundamental Research Funds for the Central Universities, and the 111 Project.

Selected Publications:
4. Libo Yuan, Tian Tian, Yufu Chen, Shengyong Yan, Xiwen Xing, Zhengan Zhang, Qianqian Zhai, Liang Xu, Shaoru Wang, Xiaocheng Weng, Bifeng Yuan, Yuqi Feng, and Xiang Zhou*, Existence of G-quadruplex structures in promoter region of oncogenes confirmed by G-quadruplex DNA cross-linking strategy, Scientific Reports, 2013, 3 : 1811 | DOI: 10.1038/srep01811.
Xiang Zhou

Prof. Xiang Zhou (Ph.D.) He received his B.S. degree from Wuhan University in 1986, M.S. from Wuhan University in 1987 (under the supervision of Professor Xuanjie Wu), and Ph.D. degree from The Chinese University of Hong Kong in 1995 (under the supervision of Professor K. S. Chan). In 1995, he joined the Department of Chemistry at University of Virginia as a research associate, in Laboratory of Professor Sidney M. Hecht. In 1996, he joined the Department of Chemistry and Biochemistry at University of Maryland, College park, as a research associate in Laboratory of Professor Steven E. Rokita. He was hired in 2001 by Wuhan University, as a full professor. In 2009, he became a Changjing Scholar Professor.

Research Interests:
Design and synthesis small molecules target DNA: recognition and interaction of nucleic acids with small molecules; the biological studies of G-quadruplex DNA; anti-tumor drug discovery, chemical epigenetics of nucleic acids.
Biological Properties of Isonucleotide (IsoNA) Modified siRNAs

Ye Huang, Yusi Wang, Miao Tian, Yue Chen, Xinneng Fan, Lihe Zhang, Zhenjun Yang
State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, Beijing 100191, China. Tel: +86-10-82802503; Email: yangzj@bjmu.edu.cn.

A variety of viral replication can be influenced by inhibitors of MAPK cascade, such as HSV2, EV71 and flu virus. It was found in HSV2 infection that MEK1-mediated activation of ERK plays an essential role in viral production. Thus specific inhibitor of MEK1 can be used in anti-HSV2 therapy while maintain the normal function of the host. In this study, we have modified a siRNA (siMek1) specific targeting MEK1 mRNA of the host, by introducing D-/L-IsoNA at position 8 and 9 in the passenger strand, to investigate the influence on RNAi potency and anti-viral effect against HSV2 and EV71. We found that siMek1-S08D could accelerate the removal of sense strand, and showed enhanced anti-viral activities. Binding free energy of RISC/ssRNA by molecular dynamic simulation indicated that the release obstacle of cleavage product of sense strand, which decreased in Ago2_S08D and increased in other three modes. By X-ray diffraction, PAZ domain is more flexible in Ago2_S08D and hard to form stable crystal structures. The interaction between modified siRNAs and Ago2 protein will be discussed. This work is supported by NIH (2012CB720604 and 2012AA022501) and NSFC (MCB-0824837 and 21332010).

Selected Publications:

Zhenjun Yang

Prof. Zhenjun Yang (杨振军) (Ph.D.), State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, Beijing 100191, China. Tel: +86-10-82802503; Email: yangzj@bjmu.edu.cn. He was born in 1964 and raised in Jilin, China. 2002-Present: Associate Professor and Professor (2008), Peiking University Health Sciences Center. 2000-2002: Postdoctoral Fellow, University of Georgia, USA. 1987-2000: Teaching Assistant, Lecturer and Associate Professor, Peking University Health Sciences Center (before April 2000, Beijing Medical University). PhD (1998): Beijing Medical University. BS (1987), Beijing Medical University. 

Research Interests: Research interest: 1. Chemical modifications and biological properties of antisense oligonucleotides, siRNAs and aptamers; 2. Antiviral and anticancer nucleoside and nucleotide analogues; 3. Cyclic nucleotide (c-di-GMP or cADPR) mimics as secondary messengers.
Macrocyclic Polyamine-Based Non-Viral Gene Vectors

Xiao-Qi Yu*

Key Laboratory of Green Chemistry and Technology (Ministry of Education), College of Chemistry, Sichuan University, Chengdu, 610064, P. R. China

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The main challenge in gene therapy is successful in vivo transfer of genetic materials to the targeted tissues. Unfortunately, a suitable vector for safe and efficient delivery of therapeutic genes into target cells is currently not yet available. Vectors for gene delivery can be divided into two classes, viral and non-viral. Non-viral vectors such as cationic polymer-DNA complexes (polyplexes) have gained a great deal of interests for their advantages including lower host immunogenicity, enabling repeated administration, higher gene carrying capacity, and easy availability even with large scales. However, the transfection efficiencies (TE) of non-viral vectors are generally much lower than the viral ones. It has been well studied that the TE is greatly dependent on a vector’s characteristics including its nitrogen profile, charge density, protonation range, molecular weight and topological structure. In our group, macrocyclic polyamines (MPA, such as cyclen and TACN) were first applied for the design and synthesis of potential gene vector materials, which include cationic lipids with MPA as hydrophilic headgroups, MPA-based linear and reticular cationic polymers, and MPA-modified gold nanoparticles. Their structure-activity relationships were systematically studied. Several materials were found to have better TE and biocompatibility than commercially available transfection reagents.

This work was supported by the National Natural Science Foundation of China (Nos. 21232005), and the National Basic Research Program of China (2012CB720603).

Selected Publications:
Xiao-Qi Yu

Prof. Xiao-Qi Yu (Ph.D.) was born in 1965 in Sichuan, China. He received his B.S. degree from Sichuan University in 1987 and Ph.D. from the same place in 1993. After graduation, he became a staff in College of Chemistry in SCU. In 1999, he was promoted as professor of SCU. In 1999-2001, he worked as a research associate in Prof. C.-M. Che’s group in Department of Chemistry, the University of Hong Kong. From 2010 to present, he is Changjiang Chair professor and Dean of College of Chemistry, SCU. He has received several awards, including Distinguished Young Scholars Awarded (2007, National Science Foundation of China), New Century Excellent Talent Award (2003, Ministry of Education of China), Outstanding Young Scientist Award (2003, Sichuan Province), Scholar Leadership Award (2006, Sichuan Province), and Excellent Teacher Awards (2001 and 2004, SCU). His research interests include biomedical materials chemistry (especially for non-viral gene and drug delivery vectors) and methodology of organic syntheses (green synthetic methodologies). He has published ~200 scientific papers on international journals including JACS, Angew. Chem. Int. Ed., Coordin. Chem. Rev., Biomaterials, Chem. Commun., Green Chem., etc.
Structural Studies of Large RNAs using Small Angle X-ray Scattering (SAXS)

Xianyang Fang1*, Edward Nikonowicz2, Yun-Xing Wang3

1The Small Angle X-ray Scattering Core Facility, Structural Biophysics Laboratory, National Cancer Institute, NIH, Frederick, Maryland, USA. Email: fangx@mail.nih.gov 2Department of Biochemistry and Cell Biology, Rice University, Houston, Texas, USA. 3The Protein Nucleic Acid Interactions Section, Structural Biophysics Laboratory, National Cancer Institute, NIH, Frederick, Maryland, USA.

The genomes of humans and other mammals were pervasively transcribed into RNAs, but no more than 3% codes for proteins, the majority are non-coding RNAs, which form complex three-dimensional (3D) structures that have key roles in a multitude of cellular processes from gene regulation to viral pathogenesis. Determination of 3D structures of RNAs are challenging and only very limited knowledge about 3D structures of RNAs is available in the PDB, which is likely due to that crystallization of RNAs with diffraction quality is extremely difficult and RNA NMR usually has a size limit. Our lab has developed a novel approach to determine the 3D structure of large RNAs based on SAXS and computation, which was firstly used to determine the topology structure of a large RNA, the HIV-1 Rev Response Element (RRE) (233 nucleotides) and answer a long-standing mystery in HIV-1 biology. The overall architecture of RRE positions the two Rev binding sites with optimal distance and orientation, which are essential for Rev binding and RRE function. The method was further utilized to determine the 3D solution structure of the full length T-box riboswitch (235nt) and its interaction with cognate tRNA, and provide insight into the mechanism of action of T-box riboswitch.

Selected Publication:
**Biography:**

Dr. Xianyang Fang was born in 1980 and raised in Hubei, China. He received his B.S. degree from Wuhan University in 2002 (under the supervision of Professor Yi Liu), and Ph.D. degree from the Institute of Biophysics, Chinese Academy of Sciences in 2008 (under the supervision of Professor Jinfeng Wang). In 2009, he joined the Protein-Nucleic Acid Interactions Section, Structural Biophysics Laboratory, National Cancer Institute, National Institute of Health as a visiting postdoctoral fellow (under the supervision of Dr. Yun-Xing Wang). He was hired as a staff (Research Fellow) of the Small Angle X-ray Scattering Core Facility, National Cancer Institute, NIH in 2013. He is the awardee of the Fellows Award for Research Excellence 2014, NIH. He has extensive experiences in structural characterization of biomacromolecules (including proteins, nucleic acids, nanostructures, protein-protein, protein-DNA, protein-RNA complexes) using SAXS and NMR in combination with other methods, and are in close collaboration with lots of research groups all over the world (such as Adrian Ferré-D’Amaré from NHLBI, NIH, and Sarah Woodson from John Hopkins University, etc). His current research interests lie generally in the areas of RNA biology, including development of novel methods for determination of 3D structure of large RNAs (long non-coding RNAs) based on SAXS, mass spectrometry, computation, development of hybrid methods for structural biology of multisubunit complexes essential to RNA metabolism, and RNA targeted drug design.
Building a Large, Diverse Encoded Library for Lead Generation

**Dr Jin Li, Chairman & CEO**

*HitGen Ltd, Chengdu 610041, China; email: Jin.Li@hitgen.com*

In this talk, we will present our design strategy in building a highly diverse, three dimensional and drug-like DNA encoded libraries (DELs) to facilitate lead-finding for novel protein target families. Library synthesis methodologies that facilitate incorporation of linking chemistry compatible with DNA integrity will be presented. Computational analysis of the resultant libraries’ molecular properties will be shown.

Validation of affinity screening, coding and decoding processes to identify known and novel enzyme inhibitors will be described, along with our early results in affinity screening of this library of >400 Million compounds with highly validated protein targets from several protein families.
Jin Li

Dr. Jin Li holds 26 years biopharmaceutical experience (at Protherics and AstraZeneca), with scientific and leadership roles in early stage research; as well as experience in initiating and leading major collaboration and outsourcing programmes. Before founding HitGen, Dr. Li held Global Director position of Compound Sciences and Computational Sciences at AstraZeneca. This included responsibility for computational chemistry, computational biology and compound collection enhancement for lead generation. Dr Li completed his BSc at Sichuan University, and PhD in macromolecular sciences at Aston University. Then Dr. Jin Li completed post-doctoral research in theoretical biochemistry at Manchester University, UK. Dr Li is also a Fellow of the Royal Society of Chemistry.
R&D of new-generation small molecule anti-acute myeloid leukemia (AML) agents

Shuang Ma, Ling-Ling Yang, Chuan Cheng, Lei Zhong, Ming-Wu Zheng, Yu Xiong, Ting Niu, Lin-Li Li, Yu-Quan Wei, and Sheng-Yong Yang*

State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University, Chengdu, Sichuan, China; email: yangsy@scu.edu.cn

FLT3 has been identified as a valid target for the treatment of acute myeloid leukemia (AML). Clinical trials of current FLT3 inhibitors treating AML showed that relapse and drug resistance are the major challenges, and leukemia stem cells (LSCs) are considered one of the most important contributors. Here, we report the characterization of SKLB-677, a new-generation FLT3 inhibitor. SKLB-677 exhibits low nanomolar potency in biochemical and cellular assays. It is efficacious in animal models at doses as low as 1 mg/kg when administrated orally once daily. In particular, SKLB-677 but not first-generation and second-generation FLT3 inhibitors in clinical trials could efficiently inhibit Wnt/β-catenin signaling; Wnt/β-catenin signaling is required for the development of LSCs, but not necessary for the development of adult hematopoietic stem cells (HSCs). Studies examining the mechanism of action indicated that SKLB-677 blocks Wnt/β-catenin signaling through down-regulation of LRP-6. Collectively, SKLB-677 is unique among the FLT3 inhibitors that are currently in clinical development because it efficiently blocks Wnt/β-catenin signaling in addition to its excellent anti-AML activity. Owing to the favorable pharmacokinetic properties, SKLB-677 represents a promising new-generation anti-AML drug candidate that not only kills AML cells but also eliminates LSCs. This work is supported by the 973 Program (2013CB967204), and National Natural Science Funds for Distinguished Young Scholar (81325021).

Selected Publications:


Sheng-Yong Yang

Prof. Sheng-Yong Yang (Ph.D.), currently works in the State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Sichuan, China. Dr. Yang got his PhD degree from Sichuan University in 1999. After that, he did his postdoc research in Hongkong University of Science and Technology from 1999-2001. In 2002-2005, he joined Prof. Tom Ziegler’s group (University of Calgary, Alberta, Canada) as a research scientist. In the end of 2005, he returned back to China. Since then, he has been working in Sichuan University. His research interests mainly focus on the methodology and applications of computer aided drug discovery (CADD). Up to now, Prof. Yang has published more than 120 papers in international journals, including JACS, Angew chem Int Ed, Leukemia, Drug Disc Today, JMC, Clin Cancer Res, JCIM et al. He has developed more than 10 methods related to CADD, and coded 6 CADD programs, including PhDD, RASA, SCADMET, GA-CG-SVM, ID-score, and TarPred. These programs have been used by many international pharmaceutical companies and academic institutes.
The Progress of Prostate Cancer Treatment

Xuehai Pang\textsuperscript{a}, Lingling Peng\textsuperscript{b}, Yu Gong\textsuperscript{c}, Yuanwei Chen\textsuperscript{bc*}; \textsuperscript{a}Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu 610041, China; \textsuperscript{b}State Key Laboratory of Biotherapy, West China Hospital, West China Medical School, Sichuan University, Chengdu, 610041, China; \textsuperscript{c}Hinova Pharmaceuticals Inc, Suite 801, Building C1, #88 South KeYuan Road, Chengdu Tianfu Life Science Park, Chengdu, 610041, China, email: ywchen@hinovapharma.com

Prostate cancer is the most common solid tumor and the second most common cause of cancer death in men worldwide, with more than 29,000 men anticipated to have died of metastatic disease in 2013 in the United States. With the rapid economic development and westernized living standard, prostate cancer incident has increased dramatically in China as well. It is estimated that prostate cancer is the number seven most common cancer incidents in male patients in China. With such great patient needs, research community has achieved great progress in this area with 5 small molecular drugs approved in the past five years. These agents include sipuleucel-T, cabazitaxel, abiraterone acetate, enzalutamide and radium-223. With more than 70 years, androgen signaling has been targeted for prostate cancer treatment. In this presentation, we will review the current progress for prostate cancer treatment and also some of our research results.

Selected Reference
Dr. Yuanwei Chen,
CEO and Founder of Hinova Pharmaceuticals Inc.

Dr. Chen is CEO and founder of Hinova Pharmaceuticals Inc, a leading drug discovery company located in Chengdu, China. Dr. Chen is also serving as professor of Chemistry at Sichuan University with the National Key Laboratory for Gene Therapy. Prior to this, Dr. Chen was the Vice President of Shanghai ChemPartner, a leading CRO organization in the world. Dr. Chen’s responsibilities include corporate business strategy, medicinal project management and business development. Dr. Chen is also serving as the GM of Chengdu ChemPartner, a wholly owned subsidiary of Shanghai ChemPartner for 5 years. Prior to ChemPartner, Dr. Chen was the Chief Scientific Officer at Egret Pharma (Shanghai) Ltd, where he was instrumental in developing drug candidate for diabetes which is currently under phase III clinical trials in US. Dr. Chen spent 4 years at Abbott Laboratories (US, Chicago) where he was involved in combinatorial chemistry and medicinal chemistry. From 1999 to 2005, he worked at the Bayer Corporation (US) on various projects in oncology, during which time he acted as project coordinator. Dr. Chen has over 20 years of experiences in pharmaceutical/outsourcing industry in US and China. He is the co-inventor of several clinical candidates and has 48 patents, and 50 research publications.

Dr. Chen received numerous award including “National 1000 Talent”, “Sichuan 1000 Talent”, “Sichuan Excellent Innovative Team”, and “10 Famous Returnees in Chengdu” etc. Dr. Chen also led and built: “Chengdu Public Analytic Platform for Pharmaceutical and biologics”, “Sichuan Generic Drug Center”. Such infrastructure greatly accelerated the development of Chengdu pharmaceutical and biotech industry.

Dr. Chen obtained PHD from University of Lausanne, Switzerland, and did postdoctoral at The Scripps Research Institute (La Jolla, US).
Recent Advances in the Synthesis and Use of Pooled Oligonucleotides
Marcello Carabalo, CustomArray, Inc. Seattle, WA, USA, Quanlai Song, Nublocks LLC, Oceanside CA, J Adams*

Azco Biotech, Inc., Oceanside, CA, USA; email: jadams@azcobiotech.com

In biology, there is increasing numbers of applications for large quantities of oligonucleotides, with oligonucleotide requirements in the millions of oligonucleotides for a single kit. However, traditional column-based synthesizers are not practical for meeting this need due to cost, about $1.00 per oligonucleotide. Recently though, there has been introduced array-based synthesizers to meet this need. With these synthesizers you can synthesize a large number of oligonucleotides on a chip, cleave them from them and collet the oligonucleotides in a “pool”. Since these synthesizers have made synthesizing very large quantities of oligonucleotides practical and cost effective, at about $0.03 per oligonucleotide or less, the need for large quantities of oligonucleotides for the increasing number of applications has been met. This paper will review the commercially available synthesizers as well as the common applications, including the development of capture baits for 2nd generation sequencing and gene synthesis for synthetic biology. The problems will be discussed as well as the approaches employed for overcoming the problems.
J O. Adams

J O. Adams is an American, currently living in San Diego, California. He received his B.S. degree in Chemistry from San Jose University in 1984, M.S. in Physical Chemistry from San Jose State University in 1986 (under the supervision of Professor Juana Acrivos). Dr. Adams also holds a Juris Doctor, earned in 2000 from Lincoln University School of Law in San Jose, California. Dr. Adams has worked in many roles in protein and nucleic acid starting his career at Genentech as an HPLC chemist in 1985, in 1987 he accepted a position at Dionex Corporation as an HPLC applications development scientist, he then developed many novel columns and applications for nucleic acid analysis and purification and was also instrumental in the development of Dionex’s automation products, in 1994, Dr. Adams went to work for Tosohas to help with the development of applications for large scale protein and nucleic acid purification, in 1997 he accepted a position with Transgenomic to focus entirely on nucleic acid synthesis and separation technologies. He worked as the business development director responsible for the acquisition and integration of Cruachem, a world leader in the development of nucleic acid synthesis reagents. In 2002, Dr. Adams founded Azco Biotech, Inc., Azco has grown to be a world leader in the area of nucleic acid synthesis. Due to increasing interest in Asia, in 2010 he opened Azco China in Changzhou, Jiangsu, China. He is currently working hard to develop unique solutions for 2nd generation sequencing and modern synthetic biology.
Crystal Structure Studies of 2'-5' -Linked RNA

Jia Sheng*, Li Li, Aaron Engelhart, Jianhua Gan, Jiawei Wang, Jack W. Szostak

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RNA can play dual roles as a carrier of genetic information and as a catalyst of specific reactions, and it may have been the first biopolymer to have emerged on the early earth. The non-enzymatic replication of RNA was likely a key step in the evolution of simple cellular life from prebiotic chemistry. In the current model of template-directed polymerization of activated monomers, the chemical copying of RNA always generates a mixture of 3'-5' and 2'-5' backbone linkages due to the similar nucleophilicity and orientation of the 2' and 3' hydroxyl groups on the ribose. This lack of regiospecificity has been regarded as a central problem for the evolution of functional RNAs, since the resulting backbone heterogeneity was expected to disrupt their folding, molecular recognition and catalytic properties of functional RNAs such as ribozymes.

However, a recent study has demonstrated that RNAs with a certain percentage of 2'-5' linkages can still retain RNA functions, e.g., in a FMN-binding aptamer and a hammerhead ribozyme system. More interestingly, it has been known for a long time that 2'-5' linkages can reduce the melting temperature of RNA duplexes, making it easier to separate the strands. Considering that strand separation is another unsolved big problem for non-enzymatic RNA replication, this feature may actually afford a selective advantage to duplexes exhibiting backbone heterogeneity. In addition, previous studies have revealed that 2'-5' linkages in a RNA duplex are more easily hydrolyzed compared to normal 3'-5' linkages. Thus, there is a selective advantage for the evolution of homogeneous RNA systems with more accurate replication. Altogether, the coexistence of 2'-5' and 3'-5' linkages may be a critical feature that allowed RNA to play a central role in the original stage of life. In this work, we will present several X-ray crystal structures of RNA duplexes and an aptamer that contain 2'-5' linkages, These structures help us to understand how RNA can adjust its structure to accommodate backbone heterogeneity.

References
Jia Sheng

Dr. Jia Sheng received his B.S. degree from Donghua University in 2002, M.S. degree from East China University of Science and Technology in 2005 under the supervision of Professor Limin Wang. Subsequently, he joined Professor Zhen Huang’s lab at Georgia State University in Atlanta as a graduate student, where he received his Ph. D. degree in bio-organic chemistry in 2009. Then he stayed in Huang lab as a postdoctoral research associate learning macromolecule X-ray crystallography for another two and half years before joining Professor Jack W. Szostak’s lab at Harvard Medical School and Massachusetts General Hospital in early 2012, where he studied 2’-5’-modified RNA structures. He joined the RNA Institute and the Department of Chemistry in State University of New York at Albany as an assistant professor in 2013. Sheng lab is currently working on the structure and function of natural RNA modifications and the development of RNA-based novel catalysts.
DNA Display for Drug Discovery

Haodong Chen, Zhuo Tang*; Nature Products Research Center, Chengdu Institute of Biology, Chinese Academy of Sciences, Chengdu, 610064, P. R. China. Email: tangzhuo@cib.ac.cn

The central problem of pharmaceutical science is the identification of small organic molecules capable of specific binding to target proteins of interest. The display of ligands such as peptides and proteins on the surface of bacteriophage (Phage display) has revolutionized the field of ligand isolation from a large library. The limitation for phage display and other in vivo display technologies such as plasmid display is the transfection efficiency, which leads to the library diversity to around $10^9$ independent molecules. Herein, a novel in vitro DNA display strategy was developed based on a new puromycin modifier. The 5′-end puromycin-tethered oligonucleotide was synthesized to hybridize mRNA, which could attack the nascent polypeptides in the process of in vitro translation. Library with more than $10^{12}$ of DNA-peptide molecules could be constructed for drug discovery. Moreover, the DNA-peptide fusion molecules could tolerate more harsh and stringent selection condition. This DNA display might therefore become a useful in vitro display technology for the selection of peptide drug candidates This work is supported by National Sciences Foundation of China (Grant No. 21172215, 21102140 and 21322208).

Selected Publications:
1. Haodong Chen, Feng Du, Gangyi Chen, Frank Streckenbach, Afshan Yasmeeen, Yun Zhao, Zhuo Tang*. Template-directed Chemical Ligation to Obtain 3′-3′ and 5′-5′ Phosphodiester DNA Linkages, Scientific Reports, 2014, 4, 4595
Zhuo Tang

Dr. Tang Zhuo was born in 1975 in China. He graduated from Sichuan University, China in 1997. He received his Ph.D. degree in Organic Chemistry from Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences in 2005. He went to University of Konstanz, Germany under the Humboldt postdoctoral research fellowships, and then McMaster University, Canada to conduct a second postdoctoral research. He started his professional career from Chengdu Institute of Biology, Chinese Academy of Sciences under the One Hundred Person Project of the Chinese Academy of Sciences in 2009. Chemical biology is a core field of his research and he is leading a group of talented scientist from the field of biology and chemistry working on nucleic acid chemistry, in vitro evolution of functional biomolecules, biosensor for genetic detection based on DNAzyme, bioinspired synthesis.
Crystal structure of integrin α4β7 complexed with Fab and small molecular drug

Yamei Yu and Timothy Springer
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Program in Cellular and Molecular Medicine, Children’s Hospital Boston and Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, 3 Blackfan Circle, Boston, MA 02115

Leukocyte recruitment in the vasculature at sites of inflammation and lymphocyte homing require multiple adhesive and signaling interactions. Most integrins mediate firm adhesion, cell spreading, and cell migration. In contrast, integrin α4β7 is specialized to mediate rolling adhesion in vivo and in vitro. α4β7 specifically recognizes MAdCAM-1 which is expressed on endothelia in mucosal tissue and Peyer’s patches, and helps target homing of lymphocytes bearing α4β7 to these sites. What features are important to the special facility of α4β7 and MAdCAM-1 compared to other integrin receptor-ligand pairs to mediate rolling interactions? Further more, both α4 integrins are promising therapeutic targets for autoimmune diseases. mAbs specific for α4 that cross-react with α4β1 and α4β7, mAbs monospecific for α4β7, and dual acting α4β1 and α4β7 small molecule antagonists have shown promising results in animal studies and clinical trials for inflammatory bowel disease, multiple sclerosis, and asthma. Determination of structures of α4β7, α4β1, and their complexes with ligands and therapeutically relevant small molecules and Fab would greatly aid in further development of therapeutics, including α4β7-specific antagonists for inflammatory bowel disease and α4β1-specific antagonists for multiple sclerosis.

Publications:
Yamei Yu

Dr. Yamei Yu was born in 1979 in Sichuan, China. She received her B.S. degree from Sichuan University in 2002 and Ph.D. degree from Peking University in 2007 (under the supervision of Professor Xiaodong Su). At the end of 2007, she joined Immune Disease Institute (now, it is merged into Boston Children’s Hospital) at Harvard Medical School as a research fellow in Laboratory of Professor Timothy Springer (a member of National Academy of Sciences). In 2013, Dr. Yu was recruited to State Key Laboratory of Biotherapy, Sichuan University, as an associate professor. She has a broad background in molecular biology and biophysics, with specific training and expertise in structural biology. Her current research interests are in structural and functional studies on bacterium effector proteins and epigenetics.
Human brain has almost $10^{11}$ neurons, and each neuron connects to 1,000 to 10,000 target cells, thereby forming a neuron forest. The connection pattern is crucial for the function of our nervous system. Each neuron develops a group of dendrites that are characteristic of its phenotype and an axon that extends to form specific pathways to reach its synaptic target. Growing axons have a highly motile structure at the growing tip called the growth cone, which "sniffs out" the extracellular environment for signals that instruct the axon which direction to grow. These signals, called guidance cues, can attract or repel axons. Growth cones contain receptors that recognize these guidance cues and interpret the signal into a chemotropic response. The general theoretical framework is that when a growth cone "senses" a guidance cue, the receptors activate various signaling molecules in the growth cone that eventually affect the cytoskeleton. Netrin is an important axon guidance cue and three receptors are identified: DCC, UNC5, and DSCAM. Our lab determined the crystal structures of extracellular Ig domains of DCC (Ref. 1) and DSCAM (unpublished data). We are trying to interpret how the receptors recognize their ligands and how the interactions transmit signals into the cells.


# Recommended by “Faculty of 1000”
Qiang Chen

Dr. Qiang Chen was born in 1978 in Tianjin, China. He received his B.S. degree and Ph.D. degree from Peking University in 2001 and 2006. In 2006, he joined Dana-Farber Cancer Institute at Harvard Medical School as a research fellow. In 2013, Dr. Chen was recruited to State Key Laboratory of Biotherapy, Sichuan University, as an associate professor. He has a broad background in molecular biology and biophysics, with specific training and expertise in structural biology. His current research interests are in structural and functional studies on molecular mechanisms of signal transduction in axon guidance, apoptosis, and epigenetics.
Structural insight into the mechanism of RNase III Action

Jianhua Gan,1,2 Brain P. Austin,1 Joseph E. Tropea,1 Gary Shaw,1 Donald L. Court,1 David S. Waugh1 and Xinhua Ji1,*

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RNA silencing, which is trigged by the introduction of dsRNA molecules, is an important gene regulation mechanism conserved in most eukaryotes. As an effective gene silencing tool, RNAi has been extensively employed in the studies of functional genomics, drug development and gene therapy. The key step of RNAi is the sequence-specific base pairing between target gene and the small RNA molecules, such as siRNAs and miRNAs.[1] In many eukaryotes, the biogenesis of the small RNA molecules depend on the dsRNA-cleavage activity of Dicer and Drosha, which are members of RNase III family proteins. While Dicer is currently the focus of intense interest,[2-3] the structurally simpler bacterial RNase III serves as a paradigm for the entire family. Here, we will present our structural studies of the RNase III from Aquifex aeolicus, which shed lights on the (1) the structural basis of dsRNA recognition, (2) the mechanism of RNA cleavage, and (3) the conformational changes between the two functional forms of RNase III.[4-7] Furthermore, we will present two new AaRNase III-RNA complex structures, which revealed a novel type RNA cleavage reaction catalyzed by RNase III.[8]

References:
Jianhua Gan

Dr. Jianhua Gan received his B.S. degree from Beijing Medical University in 1997; in 2002, he obtained his Ph.D. degree in organic chemistry from Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, under the supervision of Prof. Zongxiang Xia, learned the protein crystallography. In 2003, he went to USA and joined Prof. Xinhua Ji’s group in National Cancer Institute (NIH, USA), focusing on the structural study of protein-nucleic acid complex and proteins that can serves as novel target for drug discovery. In 2009, he joined Prof. Zhen Huang’s lab as research scientist at Georgia State University, focusing on nucleic acid–protein interaction and structure determination. In 2012, he was recruited as a professor to School of Life Sciences, Fudan University. His current research interest is in the structural studies of proteins on the RNA interference field. During his research career, he has received several awards, including the FARE Award (The Fellows Award for Research Excellence, NIH, USA) and the SER-CAT Young Investigator Award (the Southeast Regional Collaborative Access Team, USA).
Structural Insight Into the Interaction between Replicative Helicase and Primase.

Ganggang Wang¹,², Michael G Klein¹, Etienne Tokonzaba¹, Yi Zhang¹, Lauren G Holden¹, Xiaojiang S Chen¹
¹Molecular and Computational Biology, University of Southern California, 1050 Childs Way, Los Angeles, California 90089, USA; ²Key Laboratory of Environmental and Applied Microbiology, Chengdu Institute of Biology, Chinese Academy of Sciences, Chengdu, 610041, China. Email: wanggg@cib.ac.cn

Helicases are essential enzymes for DNA replication, a fundamental process in all living organisms. In bacteria, the DnaB helicases unwind duplex DNA and coordinate with RNA primase and other proteins at the replication fork. The crystal structures of hexameric DnaB reveals the hexamer forms a distinct two-layered ring structure. Monomers with two different conformations, termed cis and trans, come together to provide a topological solution for the dual symmetry within a hexamer. Structure-guided mutational studies indicate the N-terminal layer plays an important role in binding primase and regulating primase-mediated stimulation of helicase activity. This study provides insights into the structural and functional interplay between replicative helicase and DnaG primase. Moreover, the interactions of helicase/primase/ssDNA is discussed.

Selected Publications:

Biography:

Prof. Ganggang Wang (Ph.D.) was born in 1974 and raised in Shaanxi, China. He received his B.S. and M.S. degree from Sichuan University in 1996 and 1999 (under the supervision of Professor Yizheng Zhang), and Ph.D. degree from Tsinghua University in 2003 (under the supervision of Professor Zihe Rao). From 2004 to 2010, he worked as a research fellow in Laboratory of Professor Xiaojiang Chen in University of Colorado and University in Southern California. From 2010 to 2011, he worked in Laboratory of Professor Lucio Comai as a research fellow in University in Southern California. In 2011, He was hired by Chengdu Institute of Biology, Chinese Academy of Sciences. Currently, Dr Wang studied on the molecular machine in DNA replication by combination of structural and biochemical methodologies.
Facilitation of Nucleic Acid X-ray Structure Determination by Selenium Functionalization

Wen Zhang and Zhen Huang

Department of Chemistry, Georgia State University, Atlanta, Georgia, USA; email: wzhang9@gsu.edu

The elucidation of DNA and RNA structures by X-ray crystallography contribute to the understanding of molecular mechanism of DNA and RNA functions. Beside the phase determination, crystallization is the other long-standing challenge in nucleic acid X-ray crystallography. Our lab has developed the novel approach to systematically synthesize Se-DNA and Se-RNA (SeNA), in which the selenium element is able to provide the rational power to solve phase problem. More interestingly, our unique selenium mutagenesis offered the unique solution to facilitate crystallization and promote high-quality structure determination. We have experimentally and computationally investigated the mechanistic insight of the DNA crystallization facilitated by the Se-modification. We have discovered that the intramolecular and intermolecular stacking interactions mediated by the Se-functionalization have significantly increased DNA duplex stability and reduced DNA flexibility and molecular dynamics, which may play critical roles in enhancing molecular packing and DNA nucleation in crystallization. The combination of these factors may broaden the crystallization conditions and facilitate the growth and quality of crystals. Our novel discoveries suggest that in addition to phase determination, the Se-derivatization has great potential for crystallization in DNA and DNA-ligand structure study.

This work is supported by NIH (R01GM095881).

Selected Publications
1. Wen Zhang, Zhen Huang, “DNA Crystallization Facilitated by Selenium-nucleobase Stacking”, submitted
Wen Zhang

Dr. Wen Zhang is currently a research fellow at Department of Molecular Biology, Massachusetts General Hospital/Harvard Medical School. He received his B.S. degree from Tianjin University, China in Pharmaceutical Science at 2006 (under the supervision of Professor Jin-feng Wang) and Ph.D. degree from Georgia State University in Chemistry at 2012 (under the supervision of Professor Zhen Huang). He had turned postdoc associate in Professor Zhen Huang’s lab since 2012 to carry out his postdoctoral research. Dr. Zhang’s research dealt with the organic synthesis, structural biology and molecular biology of selenium modified nucleosides and nucleic acids, focusing on the Se-DNA and Se-RNA design and synthesis for nucleic acid-protein complex X-ray structural determination and development of novel nucleic acid therapeutics for disease treatment. In 2014, Dr. Zhang joined the Department of Molecular Biology at Harvard Medical School, and is working as a research fellow in the lab of Professor Jack Szostak now. His current research focuses on the exploration of the mystery of origin of life. Dr. Zhang is applying his knowledge on crystallography, molecular biology and chemistry, to study the chemical and physical processes that facilitated the transition from chemical evolution to biological evolution on the early earth. Dr. Zhang has published more than 10 scientific papers in international peer-reviewed journals, and received several patents based on the novel selenium-DNA research. He also received several fellowships and awards based on his excellent chemical and biological research.
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