Hotel for the Speakers (not from Chengdu):

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The 7th International Conference on Nucleic Acid-Protein Chemical and Structural Biology for Novel Drug Discovery

2017第七届国际核酸与蛋白质化学结构生物学创新药物研究高峰论坛

Co-Chairs:

Zhen Huang / 黄震，Xiao-Qi Yu / 余孝其，Zhi-Xiong Xiao / 肖智雄，Yuquan Wei / 魏于全

Organizers:

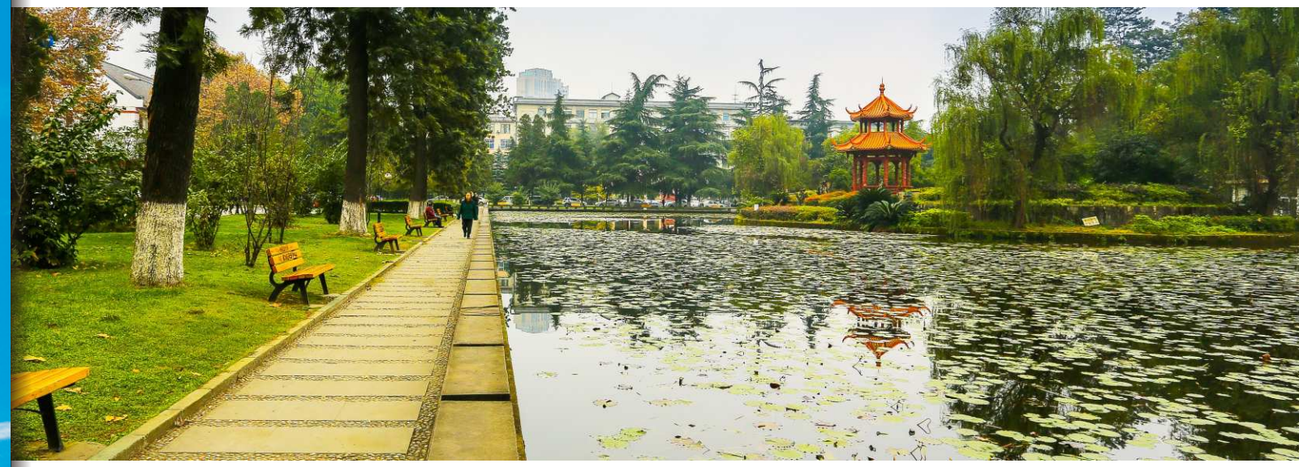
Sichuan University，College of Life Sciences / 四川大学生命科学学院
College of Chemistry / 四川大学化学学院
State Key Laboratory of Biotherapy / 四川大学生物治疗国家重点实验室
Chengdu high tech zone / 成都高新技术产业开发区
Anhui Taihe Economic and Technological Development Zone / 安徽太和经济技术开发区
Selenium Nucleic Acid Research Institute / SeNA, 硒核酸研究所

Place:

世外桃源酒店学术报告大厅 / www.cynn.cn

Time:

May 25-27, 2017 (The registration starts at 9:00 am on May 25)



四川大学

SICHUAN UNIVERSITY

四川大学是教育部直属全国重点大学，是布局在中国西部、“985工程”和“211工程”重点建设的高水平研究型综合大学。学校现任党委书记杨泉明教授、校长谢和平院士。

四川大学由原四川大学、原成都科技大学、原华西医科大学三所全国重点大学经过两次合并而成。原四川大学起始于1896年四川总督鹿传霖奉光绪特旨创办的四川中西学堂，是西南地区最早的近代高等学校；原成都科技大学是新中国院系调整时组建的第一批多科型工科院校；原华西医科大学源于1910年由西方基督教会组织在成都创办的华西协合大学，是西南地区最早的西式大学和国内最早培养研究生的大学之一。1994年，原四川大学和原成都科技大学合并为四川联合大学，1998年更名为四川大学，江泽民、李鹏等党和国家领导人就两校合并为学校题词并寄予深切厚望。2000年，四川大学与原华西医科大学合并，组建了新的四川大学。李岚清同志在考察新四川大学时说：“四川大学是我们改革最早的大学，对我国高校的改革做出了历史性的贡献，可以说是高校体制改革的先锋。”在2008年“5·12”汶川特大地震抗震救灾期间，吴邦国、温家宝等党和国家领导人先后到四川大学视察慰问。

四川大学学科门类齐全，覆盖了文、理、工、医、经、管、法、史、哲、农、教、艺等12个门类，有30个学科型学院及研究生院、海外教育学院等学院。现有博士学位授权一级学科44个，博士学位授权点277个，硕士学位授权点361个，专业学位授权点32个，本科专业131个，博士后流动站33个，国家重点学科46个，国家重点培育学科4个，是国家首批工程博士培养单位。

锦江黉门，弦歌铿锵。展望未来，四川大学将始终肩负集思想之大成、育国家之栋梁、开学术之先河、促科技之进步、引社会之方向的历史使命与社会责任，再谱中国现代大学继承与创造并进、光荣与梦想交织的辉煌篇章！

ONE OF THE CHINA 8 SCHOOLS — SICHUAN UNIVERSITY

Sichuan university is a national key university directly under the ministry of education, is the layout in the west of China, the \"985 project\" and \"211 project\" key construction of high level comprehensive research university. The incumbent party secretary Yang Quanming at school, the principal Xie Heping academicians.

The former sichuan university, sichuan university, chengdu university of science and technology three former huanan west medical university after a merger of two national key university. The original sichuan university began in the 1896 sichuan governor LuChuanLin in guangxu purport of Chinese and western school founded by sichuan, southwest is the earliest modern institutions of higher learning; The former chengdu university of science and technology department of the People's Republic of China is to adjust the form of the first type multidisciplinary engineering colleges and universities; Former huanan west medical university from 1910 by the western Christian church organization founded in chengdu huaxi xiehe university, is the first western-style university in southwest China and one of the earliest train graduate university. In 1994, the original sichuan university and the former chengdu university of science and technology into sichuan union university, in 1998 changed its name to the sichuan university, jiang zemin, li peng, and other party and state leaders on the two schools merged inscription and deep expectation for the school. In 2000, sichuan university merged with former huanan west university of medical sciences, has formed a new sichuan university. Comrade li lanqing in examining the new sichuan university, said: \"is that we reform the earliest university, sichuan university made a historic contribution to the reform of colleges and universities in China, can be said to be the pioneer of the system reform of colleges and universities.\" In 2008 \"5 · 12\" wenchuan earthquake during the earthquake relief, wu bangguo, wen jiabao, the premier, and other party and state leaders have visited condolences to sichuan university.

Sichuan university disciplines to be complete, covering the arts, science, engineering, medicine,, tubes, law, history, philosophy, agriculture, teaching, art, such as 12 categories, there are 30 subject college and graduate school, the school of overseas education college. Existing doctorate authorization first-level discipline 44, doctor's degree authorization centers, 277, 361 master's degree authorization centers, professional degree authorization centers, 32, 131 undergraduate majors, 33 post-doctoral mobile stations, 46 national key disciplines, four countries cultivate disciplines, is the country's first project unit of PhD graduates.

Jinjiang HongMen a long history, system. Looking to the future, sichuan university will always take thought of, nurtures the pillar of the country, is the first academic, promote the progress of science and technology, society lead the direction of historical mission and social responsibility, to inherit and create hand in hand, spectrum Chinese modern college glory and dream weaving brilliant chapter!





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Sichuan University / 四川大学

Keynote Speaker: Jack Szostak / 2009诺贝尔医学奖得主

Time:
May 25–27, 2017

Place:
Lecture Hall in Cynn Hotel

Co-Chairs:
Zhen Huang / 黄震
Xiao-Qi Yu / 余孝其
Zhi-Xiong Xiao / 肖智雄
Yuquan Wei / 魏于全

Committee Members:
Yuquan Wei / 魏于全
Zhi-Xiong Xiao / 肖智雄
Xiao-Qi Yu / 余孝其
Yuanwei Chen / 陈元伟
Jin Li / 李进
Xiankai Kong / 孔宪凯
Luoting Yu / 余洛汀
Zhen Huang / 黄震

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Conference Agenda

Thursday, May 25, 2017

Registration & Meeting 9:00 – 22:00	**Registration** at Cynn Hotel (世外桃源酒店:www.cynn.cn); check-in and visit Chengdu City or Sichuan University (in the morning or early afternoon); **Ms. Yang Zhang** (contact): Tel.: 138-8176-5181; Email: zhangyang_scu@163.com
17:30 – 19:00	**Speakers' and Guests' Buffet Dinner** Dining Hall on the first floor of Cynn Hotel
19:00 – 21:30	**Reception, Poster Presentation, & Social Hour;** **Host: Zhen Huang** (三楼芙蓉厅; Furong Hall, 3F Third Floor)

Friday, May 26 （百合厅 B; Third Floor, Baihe Hall B ） Chair: Xiao-Qi Yu

7:30-8:20	Welcome and Registration （世外桃源酒店）
8:20 – 8:45	Welcome & Opening Speech: **Yu-Quan Wei** (Vice President of Sichuan University) and others from Sichuan University, Chengdu City and Taihe High-Tech/Economic Zone（世外桃源酒店，百合厅B; Baihe Hall ）
8:45- 9:30	Keynote Speech: **Jack Szostak** (2009 Nobel Laureate in Medicine or Physiology), Harvard Medical School, Massachusetts General Hospitat, “The Surprising Chemistry of Nonenzymatic RNA Replication”
9:30 – 10:00	**Steven Benner,** Foundation for Applied Molecular Evolution, "Detection, Surveillance, and Diagnosis of Multiple Pathogens At Points-of-Sampling”
10:00 – 10:30	**Zhixiong Xiao,** Sichuan University, " Metformin Induces Cancer Cell Anoikis via inhibition of Epithelial Protein ΔNp63α independent of AMPK”
10:30 – 11:00	**Speaker Group Photo and Coffee/Tea Break** **Chair: Zhi-Xiong Xiao**
11:00 – 11:30	**Lihe Zhang,** Peking University, “Identifying Glyceraldehyde 3-Phosphate Dehydrogenase as a Cyclic Adenosine Diphosphoribose （cADPR） Binding Protein by Photoaffinity Protein-Ligand Labeling Approach”
11:30 – 12:00	**Ming Chen,** ZheJiang University, "The role of epigenetic factors in long-range interactions and stress response”
12:00 – 13:30	**Speakers' Buffet Lunch in Hotel** **Chair: Yuanwei Chen**
13:30 – 14:15	**David M. J. Lilley,** University of Dundee, "Multiple catalytic strategies of the nucleolytic ribozymes”
14:15 – 14:45	**Daiwen Yang,** National University of Sigapore, "Structural basis for DNA unwinding by human PUR-α”
14:45 – 15:15	**Gang Chen,** Nanyang Technological University, "Targeting Double-Stranded RNA Structures by a Peptide Nucleic Acids Platform”
15:15 – 15:45	**Zhen Huang,** "Selenium Atom-specific Functionalization of Nucleic Acids for Structure and Function Studies”
15:45 – 16:15	**Coffee/Tea Break** **Chair: David Lilley**
16:15 – 16:45	**Yuanwei Chen,** "The Discovery of a Novel Androgen Receptor for the Treatment of Prostate Cancer"
16:45 – 17:15	**Shan-Ho Chou,** National Chung Hsing University, "Cyclic-di-AMP Exhibits Distinct Binding Mode to Cyclic-di-GMP in Exhibiting Different Roles in Bacterial Pathogenicity"
17:15 – 17:45	**Xinjing Tang,** Peking University, "Photomodulating the Functions of Nucleic Acids/Protein Complexes with Caged Oligonucleotides”
18:00 – 20:30	**18:00 – 20:30 Speakers' Banquet in Hotel** (3F百合厅A; Baihe A)

Saturday, May 27 (3F芙蓉厅; Furong Hall) Chair: Ioan Andricioaei

8:30 – 9:00	**Liang Tong,** Columbia University, "mRNA processing, decay and quality control in eukaryotes"
9:00 – 9:30	**Benjamin L. Miller,** University of Rochester Medical Center, "A General, Modular Strategy for Small Molecule – RNA recognition"
9:30 – 10:00	**Xiaojie Cui,** Institut Curie, "Non-Canonical G-quadruplexes Trigger hCEB1 Minisatellite Instability in Saccharomyces cerevisiae"
10:00 – 10:30	**Coffee/Tea Break** **Chair: Steven Benner**
10:30 – 11:00	**Juewen Liu,** University of Waterloo, "In vitro Selection of New Metal-Specific RNA-cleaving Deoxyribozymes"
11:00 – 11:30	**Chaoyong Yang,** Xiamen University, "Aptamer Functionalized Microfluidic Device for Synergistic Enrichment of Circulating Tumor Cells"
11:30 – 12:00	**Sik Lok Lam,** University of Hong Kong, "The Roles of DNA Mini-dumbbell in Repeat Expansions"
12:00 – 13:30	**Speakers' Buffet Lunch in Hotel** **Chair: Benjamin Miller**
13:30 – 14:00	**Jin Li,** "DNA-encoded libraries (DELs) for lead generation: its impact and recent developments"
14:00 – 14:30	**Mark Fisher,** St George's University of London, "Structural basis of DNA capture and gating by gyrase and topoisomerase IV and its inhibition by antibacterial therapeutics"
14:30 – 15:00	**Zhongzhou Chen,** Chinese University of Agriculture, "Mechanistic insights into metal ion activation and operator recognition by the ferric uptake regulator"
15:00 – 15:30	**Ioan Andricioaei,** University of California (Irvine), "Functional Roles of Local and Global Motions in Nucleic Acids"
15:30 – 15:45	Poster Award and Closing Remarks
17:00 – 20:30	**Speakers' Dinner in City**

TITLE

The Surprising Chemistry of Nonenzymatic RNA Replication

Jack W. Szostak*, Professor of Genetics and Professor of Chemistry and Chemical Biology, Harvard University and Massachusetts General Hospital, Boston, MA, 02115 USA;
Email: szostak@molbio.mgh.harvard.edu

Abstract:

The ability to copy short RNA templates without enzymes is important for the synthesis of model protocells that mimic the proposed structure of primitive cells on the early Earth. Several recent developments have enhanced our ability to copy RNA templates. We used both thermodynamic and kinetic studies to demonstrate an important catalytic role for activated downstream nucleotides and oligonucleotides in the addition of an activated monomer to a primer. We subsequently showed that this catalytic effect was due to the formation of a covalent imidazolium-bridged dinucleotide intermediate in primer extension. Mechanistic studies then led to the identification of 2-aminoimidazole as a superior nucleotide activating moiety. In addition, replacing the canonical U monomer with 2-thio-U allows for faster and more accurate template copying. The combination of 2-thio-U with 2-aminoimidazole activated monomers and helper trinucleotides enables the rapid and accurate copying of short mixed sequence templates.

Biography:

Prof. Jack W. Szostak received his B.Sc. from McGill University in Montreal in 1972, and then conducted his graduate research under the supervision of Prof. Ray Wu at Cornell University, Ithaca, NY, obtaining his Ph.D. in 1977. Dr. Szostak then moved to the Sidney Farber Cancer Institute and Harvard Medical School in 1979, and then to Massachusetts General Hospital in 1984. During the 1980s he carried out research on the genetics and biochemistry of DNA recombination, which led to the double-strand-break repair model for meiotic recombination. At the same time Dr. Szostak made fundamental contributions to our understanding of telomere structure and function, and the role of telomere maintenance in preventing cellular senescence. For this work Dr. Szostak shared, with Drs. Elizabeth Blackburn and Carol Greider, the 2006 Albert Lasker Basic Medical Research Award and the 2009 Nobel Prize in Physiology or Medicine.

In the 1990s Dr. Szostak and his colleagues developed in vitro selection as a tool for the isolation of functional RNA, DNA and protein molecules from large pools of random sequences. His laboratory used in vitro selection and directed evolution to isolate and characterize numerous nucleic acid sequences with specific ligand binding and catalytic properties. For this work, Dr. Szostak was awarded, along with Dr. Gerald Joyce, the 1994 National Academy of Sciences Award in Molecular Biology and the 1997 Sigrist Prize from the University of Bern. In 2000, Dr. Szostak was awarded the Medal of the Genetics Society of America, and in 2008 Dr. Szostak received the H.P. Heineken Prize in Biophysics and Biochemistry.

From 2000 until the present Dr. Szostak's research interests have focused on the laboratory synthesis of self-replicating systems and the origin of life. For this work he received the Harold Urey Medal from the International Society for the Study of the Origin of Life in 2011.

Dr. Szostak is an Investigator of the Howard Hughes Medical Institute, Professor of Genetics at Harvard Medical School, Professor of Chemistry and Chemical Biology at Harvard University, and the Alex Rich Distinguished Investigator in the Dept. of Molecular Biology and the Center for Computational and Integrative Biology at Massachusetts General Hospital. Dr. Szostak is a member of the National Academy of Sciences and the American Philosophical Society, and a Fellow of the New York Academy of Sciences, the American Academy of Arts and Sciences, and the American Association for the Advancement of Science.

TITLE

Detection, Surveillance, and Diagnosis of Multiple Pathogens At Points-of-Sampling

Steven A. Benner, Zunyi Yang, and Zhen Huang；Foundation for Applied Molecular Evolution, Alachua, Florida, USA Firebird Biomolecular Sciences LLC, Alachua, Florida, USA；SeNtInAll, Chengdu, Sichuan China

Abstract：

Reagents, devices, and device architectures are emerging from Firebird Biomolecular Sciences LLC and the Foundation for Applied Molecular Evolution to support the detection of nucleic acids from pathogens. These pathogens include the mosquito-borne Zika and dengue viruses, tick-borne bacteria that cause Lyme disease, and sexually transmitted diseases such as human papilloma virus (HPV). Additional projects have been funded to analyze fungal pneumonia and gastrointestinal diseases. These technologies include:

- An artificially expanded genetic information systems (AEGIS), which delivers ultra-clean detection of pathogen nucleic acids.
- A self-avoiding molecular recognition system (SAMRS) that supports essentially unlimited multiplexing in assays that detect pathogen nucleic acids.
- Device architectures that allow detection of pathogen nucleic acids in 30 minutes without PCR and in the hands of operators who need no clinical certification, at costs less than $10.00.
- Reversible terminators that allow detection and quantitation of variant pathogen nucleic acids.

SeNtInAll, based in Chengdu, is initiating a broad analysis of the market in China for assays that have these specifications, to determine which pathogen targets will be most important to improve the health of the residents of Sichuan Province, and what device architectures will be most easily used by individuals responsible for that health. As part of this work, SeNtInAll will be receiving samples from individuals wishing to provide surveillance of pathogens in the environment, and providing diagnostics advice to patients possibly infected by these pathogens and their caregivers.

Biography:

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 Z ü rich, 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.

TITLE

Metformin Induces Cancer Cell Anoikis via inhibition of Epithelial Protein ΔNp63α independent of AMPK

Yong Yi and Zhi-Xiong Jim Xiao*, Professor and Director of Center of Growth, Metabolism and Aging, College of Life Sciences, Sichuan University, Chengdu, Sichuan 610065, China; Email: jimzx@scu.scu.edu.cn

Abstract:

The blood-glucose modifier metformin is used to treat type II diabetes and has also been shown to possess anti-cancer activities. Recent studies indicate that glucose deprivation can greatly enhance metformin-mediated inhibition of cell viability, but the molecular mechanism involved in this inhibition is not yet clear. In this study, we show that under glucose deprivation, metformin inhibits expression of ΔNp63α, a p53 family member involved in cell adhesion pathways, resulting in disruption of cell-matrix adhesion and in subsequent apoptosis in human squamous carcinoma cells. We further show that metformin promotes ΔNp63α protein instability independent of AMP-activated protein kinase and that WWP1, an E3 ligase of ΔNp63α, is involved in metformin-mediated down-regulation of ΔNp63α levels. In addition, we demonstrate that a combination of metformin and the glycolysis inhibitor 2-DG significantly inhibits ΔNp63α expression and also suppressed xenographic tumor growth in vivo. In summary, this study reveals a new mechanism that down-regulation of ΔNp63α leads to disruption of cell-matrix adhesion program contributes to metformin-mediated anticancer activity and suggests a new strategy in treating human squamous cell carcinoma.

Work is supported by National Natural Science Foundation of China [81330054 and 81520108020] and by Ministry of Science and Technology of China [2012CB910700].

Selected Publications:

- Linshan Hu, Shan Liang, Hu Chen, Tao Lv, Junfeng Wu, Deshi Chen, Min Wu, Shengnan Sun, Haibo Zhang, Han You, Hongbin Ji, Yujun Zhang, Johann Bergholz, and Zhi-Xiong Jim Xiao*, ΔNp63α is a common inhibitory target in oncogenic PI3K/Ras/Her2-induced cell motility and tumor metastasis. PNAS, in press. doi/10.1073/pnas.1617816114
- Yi Y, Chen D, Ao J, Sun S, Wu M, Li X, Bergholz J, Zhang Y, Xiao ZX*. Metformin Promotes AMP-activated Protein Kinase-independent Suppression of ΔNp63α Protein Expression and Inhibits Cancer Cell Viability. J Biol Chem. 2017 Mar 31;292(13):5253-5261. doi: 10.1074/jbc.M116.769141. Epub 2017 Feb 13.
- He H, Wang C, Dai Q, Li F, Bergholz J, Li Z, Li Q, Xiao ZX* (2016) p53 and p73 Regulate Apoptosis but Not Cell-Cycle Progression in Mouse Embryonic Stem Cells upon DNA Damage and Differentiation. Stem Cell Reports. 7(6):1087-1098. doi: 10.1016/j.stemcr.2016.10.008. Epub 2016 Nov 17
- Xinni Jiang, MengMeng Niu, Deshi Chen, Jing Chen, Yang Cao, Xiaorong Li, Haoqiang Ying, Johann Bergholz, Yujun Zhang, Zhi-Xiong Xiao (2016) Inhibition of Cdc42 is essential for Mig-6 suppression of cell migration induced by EGF. Oncotarget, 7:49180-193. doi: 10.18632/oncotarget.10205
- Linshan. Hu, Haibo Zhang, Johann Bergholz, Shengnan Sun, and Zhi-Xiong Xiao (2016) MDM2/MDMX: Master negative regulators for p53 and RB, Molecular & Cellular Oncology, 3:2016
- H Zhang, L Hu, W Qiu, T Deng, Y Zhang, J Bergholz and Z-X Xiao* (2015) MDMX exerts its oncogenic activity via suppression of retinoblastoma protein. Oncogene, 34, 5560-5569 (29 October 2015) | doi:10.1038/onc.2015.11doi:10.1038/onc.2015.11
- Tong Y, Ying H, Liu R, Li L, Bergholz J, Xiao ZX* (2015) Pin1 inhibits PP2A-mediated Rb dephosphorylation in regulation of cell cycle and S-phase DNA damage. Cell death & disease 6:e1640. doi: 10.1038/cddis.2015.3.
- J Bergholz1, Y Zhang, J Wu, L Meng, EM Walsh, A Rai, MY Sherman and Z-X Xiao*.(2014)ΔNp63αregulates Erk signaling via MKP3 to inhibit cancer metastasis. Oncogene 33, 212–224.
- Wang, Yujun Zhang, Qintong Li, James L. Kirkland and Zhi-Xiong Xiao* (2014) Insulin-like growth factor-1 regulates the SIRT1-p53 pathway in cellular senescence. Aging Cell (2014) pp1–10, Doi: 10.1111/acel.12219

Biography:

Zhi-Xiong Jim Xiao, (肖智雄) PhD
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1991-1996, Postdoctor, at Harvard Medical School, Dana-Farber Cancer institute, 1996- 2010, Assistant Professor, Associate Professor, and Professor, Departments of Biochemistry/Medicine, Boston University School of Medicine 2010- Present, National Distinguished Professor, College of Life Sciences, Sichuan University, Chengdu, China; Adjunct Professor of Biochemistry, Boston University School of Medicine, Director, Center of Growth, Metabolism and Aging, Sichuan University; Chief Scientist, National Key Research Program (973) for “Signaling Network and Cancer Metastasis” Editor, Cell Death and Diseases

My lab has been working on the function and regulation of p53 family and Rb in tumorigenesis. Current focuses are the role of p53-related p63 in cell adhesion pathway and cancer metastasis; energy stress and cancer metabolism; signaling in aging; stem cell biology; small molecules in cancer treatment.

TITLE

Identifying Glyceraldehyde 3-Phosphate Dehydrogenase as a Cyclic Adenosine Diphosphoribose （cADPR） Binding Protein by Photoaffinity Protein−Ligand Labeling Approach

Prof. Li He Zhang

Abstract:

Cyclic adenosine diphosphoribose (cADPR), an endogenous nucleotide derived from nicotinamide adenine dinucleotide (NAD+), mobilizes Ca2+ release from endoplasmic reticulum (ER) via ryanodine receptors (RyRs), yet the bridging protein(s) between cADPR and RyRs remain(s) unknown. Here we synthesized a novel photoaffinity labeling (PAL) cADPR agonist, PALcIDPRE, and subsequently applied it to purify its binding proteins in human Jurkat T cells. We identified glyceraldehyde 3-phosphate dehydrogenase (GAPDH) as one of the cADPR binding protein(s), characterized the binding affinity between cADPR and GAPDH in vitro by surface plasmon resonance (SPR) assay, and mapped cADPR's binding sites in GAPDH.

Ref.

- **The Chemical Record, 2015,15(2),511-523**
- **J. Am. Chem. Soc. 2017, 139, 156−170**

Biography:

LI-HE, ZHANG, BoYa Chair Professor, Peking University, Beijing , China. Now he is working in State Key Laboratory of Natural & Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University. He graduated from Department of Pharmacy, Beijing Medical College in 1958 and got graduate diploma of medicinal chemistry in 1967 from the same college. He worked in Department of Chemistry, University of Virginia, USA, as research associate from 1981-1983. In 1985, he became professor of medicinal chemistry in School of Pharmaceutical Sciences, Beijing Medical University and was appointed dean of School of pharmaceutical Sciences, Beijing Medical University (1987-1999) and Director of Chemistry Division of National Natural Science Foundation of China (1999-2006). He is the Member of Chinese Academy of Sciences (1995)； Titular Member, IUPAC, Division III , Organic and Biomolecular Chemistry Committee (2006-2008);Fellow IUPAC (2016-)： Fellow, Royal Society of Chemistry, UK (2006-), and is on the Editorial boards of a number of scientific journals including Medicinal Research Reviews, Current Topics in Medicinal Chemistry and Organic & Biomolecular Chemistry, ChemmedChem. He now is Editor Associate of Eur. J. Med. Chem. His research interests include chemistry of nucleosides and nucleotides, anticancer and antiviral drugs. He got many Scientific Awards including National Second Class Award in Natural Science (2004;2014).

TITLE

The role of epigenetic factors in long-range interactions and stress response

Authors: Jingjing Wang, Xianwen Meng, Yingcong Zhou, Xue Li, and Ming Chen*

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Keys worlds: epigenetic regulation, long-range interactions, stress response, lncRNA

Abstract :

The epigenetic mechanisms, including histone modifications, DNA cytosine methylation, histone variants and non-coding RNAs (ncRNAs), play a key role in determining transcriptional outcomes. We outlined a framework to study different epigenetic mechanisms working with each other in Arabidopsis and explored the mutual regulation between chromatin marks and non-coding RNAs in various ways. Three-dimensional shapes of chromosomes regulate gene expression and genome function. We integrated data of 17 epigenetic marks and 35 transcription factors and identified seven groups of interacting loci, which can be distinguished by their epigenetic profiles. These seven groups of interacting loci can be divided into three types of chromatin linkages based on expression status. We observed that two interacting loci sometimes share common epigenetic and transcription factor binding profiles. Different groups of loci display very different relationships between epigenetic marks and the binding of transcription factors. Distinctive types of chromatin linkages exhibit different gene-expression profiles. Our study unveils an entirely unexplored regulatory interaction, linking epigenetic profiles, TFs binding and the three-dimensional spatial organization of the Arabidopsis nuclear genome.

In addition, accumulating evidence indicates ncRNAs, especially microRNAs (miRNAs) and long ncRNAs (lncRNAs), have emerged as key regulatory molecules in plant stress responses. Therefore, we summarized current progresses on the understanding of plant miRNA and lncRNA identification, characteristics, bioinformatics tools, resources, and provided examples of mechanisms of miRNA- and lncRNA-mediated plant stress tolerance. We presented the identification and characterization of lncRNAs under seven nutrient stress conditions. The expression pattern analysis revealed that aberrant expression of lncRNAs is a stress-specific manner under nutrient stress conditions, and that lncRNAs are more sensitive to nutrient stress than protein coding genes (PCGs). Moreover, competing endogenous RNA (ceRNA) network and lncRNA-mRNA CEN were constructed to explore the potential function of these lncRNAs under nutrient stress conditions. We further combined different expressed lncRNAs with ceRNA network and CEN to selected key lncRNAs in response to nutrient stress. Our study may provide important information for further insights into the role of lncRNAs in response to stress in plants.

Biography:

Prof.Ming Chen received his PhD in Bioinformatics from Bielefeld University, Germany, in 2004. Currently he is working as a full professor at Zhejiang University. His group research work mainly focuses on the systems biology, computational and functional analysis of transcriptomics, proteomics and bioinformatics research and application for plant sciences. Prof. Chen is serving as an academic leader in Bioinformatics at Zhejiang University. He chairs the Bioinformatics Society of Zhejiang Province, China. He serves as a committee member of Chinese Societies for "Functional Genomics & Systems Biology", "Computational Systems Biology" and "Biomedical Information Technology".

TITLE

Multiple catalytic strategies of the nucleolytic ribozymes

David M. J. Lilley 李大卫
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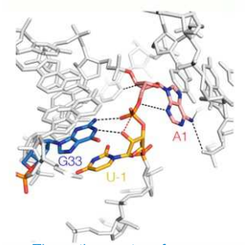
Abstract:

The nucleolytic ribozymes employ multiple processes that contribute to catalysis - (1) facilitation of an in-line trajectory, (2) stabilization of the phosphorane transition state, (3) activation of the O2' nucleophile, and (4) facilitation of the departure of the leaving group. There are multiple ways in which ribozymes achieve this. The twister ribozyme exhibits all four processes to accelerate its cleavage reaction. It uses general acid-base catalysis, mediated by the nucleobases of G33 and A1 as general base (process 4) and acid (process 3) respectively. The latter is highly unusual, as A1 is located immediately 3' to the scissile phosphate, using its highly acidic N3 as the proton donor. A 100-fold stereospecific phosphorothioate effect at the scissile phosphate is consistent with a significant stabilization of the transition state (process 1) by interaction of G33 N2 with the scissile phosphate. A1 is accommodated in a specific binding pocket that raises its pKa towards neutrality, juxtaposes its N3 with the O5' to be protonated (process 4), and helps create the in-line trajectory required for nucleophilic attack (process 2). Thus the entire structure of the ribozyme has evolved to generate the local environment that promotes catalysis. By contrast, our new mechanistic and structural studies of the TS ribozyme reveal this to function as a metalloenzyme. We propose a new classification of the nucleolytic ribozymes according to their catalytic mechanisms.



The active center of the twister ribozyme

T. J. Wilson and D. M. J. Lilley The evolution of chemistry in the ribozymes. Science 323, 1436-1438 (2009).

Y. Liu, T. J. Wilson, S. A. McPhee and D. M. J. Lilley. Crystal structure and mechanistic investigation of the twister ribozyme Nature Chem. Biol. 10, 739-744 (2014).

T. J. Wilson, Y. Liu, C. Domnick, S. Kath-Schorr and D. M. J. Lilley The novel chemical mechanism of the twister ribozyme J. Amer. Chem. Soc. 138, 6151–6162 (2016).

Y. Liu, T. J. Wilson and D. M. J. Lilley The structure of a nucleolytic ribozyme, with an important role for a catalytic metal ion Nature Chem. Biol. In the press.

Biography:

Prof. David Lilley FRS is director of the CRUK Nucleic Acid Structure Research Group at the University of Dundee. He is interested in the structure, dynamics and activities of nucleic acids, both DNA and RNA. His laboratory uses structural (predominantly X-ray diffraction), biophysical (fluorescence, especially on single molecules) and biochemical approaches, combined with a strongly mechanistic viewpoint.

In DNA, Lilley solved the structure of the four-way DNA (Holliday) junction, and has made extensive studies of the manner of their interactions and recognition by junction-resolving enzymes. The basic recognition processes have been defined in bacterial and phage enzymes, but now the work has been extended to include the eukaryotic enzymes GEN1 and SLX1/SLX4. He has recently solved the structure of eukaryotic GEN1 bound to DNA.

In RNA Lilley has long advocated the view that complex structure can be reduced to rigid helical elements jointed by junctions that determine the trajectory. In the last decade he has made detailed studies of the kink-turn element to the point where this is now arguable the best-understood such motif. He has generated a set of rules for kink-turn folding that have strong predictive power, and can be applied to new RNA sequences as they emerge. In additional to structural elements, Lilley has made detailed mechanistic and structural studies of RNA catalysis, particularly seeking chemical explanation of the origins of these catalysts. He has particularly characterized the mechanisms of general acid-base catalysis in the hairpin, VS, hammerhead and most recently the twister ribozyme.

Along the way, Lilley has been involved in the development of fluorescence resonance energy transfer (FRET) as a structural tool in nucleic acids. His 1989 paper in Nature studying the structure of the four-way DNA junction was the first of the modern era of FRET. Since then this has been applied extensively in single-molecule studies and most recently Lilley has developed the analysis of the k2 parameter to provide orientational information, and as an additional benefit, improved distance information.

李大卫有很多联系跟中国。他是厦门大学的客座教授。在上海复旦大学他有合作的研究经费。在北京和武汉他也有联系。

TITLE

Structural basis for DNA unwinding by human PUR-α

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Abstract:

Purine-rich element-binding proteins (PUR) have been shown to be involved in many cellular processes. They perform functions through interacting mainly with nucleic acids such as guanine rich single-stranded (ss) DNA and RNA. PUR-α is a member of the PUR family. In human, mutations in PUR-α cause severe neurodevelopmental delay, learning disability, neonatal hypotonia, seizures, and encephalopathy. PUR-α has also been shown to stimulate replication of HIV-1 and JCV viruses. Eukaryotic PUR proteins consist of three repeats (I, II, and III). Previous structural studies focused on Drosophila PUR-α which shares a low amino acid sequence similarity with human PUR-α and also displays distinct RNA/DNA-binding properties from the human protein. Here, we present the NMR structure of repeats I-II of human PUR-α in complex with a ssDNA. The two repeats, which fold into an intramolecular dimer, bind to one ssDNA rather than two as shown by the structure and DNA titration monitored by fluorescence. Repeat III, which exists as a homodimer, also binds to one ssDNA. The structure reveals new insights into how the protein unwinds double-stranded DNA.

This work is supported by CNSF 21190041, K.C.Wong Education Foundation, and Singapore Ministry of Education (Academic Research Fund Tier 3, MOE2012-T3-1-008).

Biography:

Prof. Daiwen Yang obtained his PhD from Wuhan Institute of Physics, Chinese Academy of Sciences in 1991. He had his postdoctoral training at ERATO, Japan and the University of Toronto, Canada. He worked as a senior research associate at the University of Toronto before joining National University of Singapore as an assistant professor in 2001. His laboratory is interested in development and application of NMR and computational methodology for the characterization of protein structure and dynamics. One of his current research focuses is structural basis of nucleic-acid recognition by proteins.

TITLE

Targeting Double-Stranded RNA Structures by a Peptide Nucleic Acids Platform

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Abstract :

As double-stranded RNA stem regions are often involved in biologically important tertiary triplex structure formation and protein binding, the ability to sequence-specifically target any desired RNA duplexes would have great potential for biomedical applications. We are developing a new four-letter chemical code (T, L, S, and F) for the recognition of RNA Watson-Crick duplexes. RNA duplexes with any Watson-Crick pairs (AU, GC, UA, or CG) can be recognized by forming T-AU, L-GC, S-UA, and F-CG base triples, respectively. The four bases are grafted on the Peptide Nucleic Acid (PNA) with an unnatural peptide-like backbone. Remarkably, the triplex-forming PNAs can specifically and selectively bind to RNA duplex over single-stranded RNA and double-stranded DNA regions. Compared to a traditional antisense strand, which forms a duplex structure with the target sequence, the advantages of a triplex-forming PNA are as follows: (1) The triplex formation strategy facilitates the targeting of not only the sequence but also the secondary structure of RNA, which results in high selectivity. (2) The triplex formation does not involve the disruption of the pre-formed RNA secondary structure of the target sequence, which presumably facilitates fast binding kinetics. Compared to small molecule binders, triplex-forming PNAs are advantageous for sequence-specifically binding to RNA duplex structures and can do so in a programmable manner. In this presentation, I will present our results on the synthesis and biophysical characterization of the dsRNA-binding PNAs. I will further discuss the biological applications of the PNAs platform in targeting biomedically important RNA structures including a pre-mRNA splice site structure, microRNA precursors, a bacterial ribosomal frameshifting stimulatory mRNA structure, and viral RNA structures.

Work is supported by Singapore Ministry of Education (MOE) Tier 2 grants [MOE2013-T2-2-024 and MOE2015-T2-1-028].

Selected Publications:

- Zhensheng Zhong, Lixia Yang, Haiping Zhang, Jiahao Shi, J. Jeya Vandana, Do Thuy Uyen Ha Lam, René C. L. Olsthoorn, Lanyuan Lu, and Gang Chen,* Mechanical unfolding kinetics of the SRV-1 gag-pro mRNA pseudoknot: possible implications for −1 ribosomal frameshifting stimulation, Sci Rep, 2016, Accepted.
- Desiree-Faye Kaixin Toh, Gitali Devi, Kiran M. Patil, Qiuyu Qu, Manikantha Maraswami, Yunyun Xiao, Teck Peng Loh, Yanli Zhao,* and Gang Chen,* Incorporating a Guanidine-Modified Cytosine Base into Triplex-Forming PNAs for the Recognition of a C-G Pyrimidine-Purine Inversion Site of an RNA Duplex, Nucleic Acids Res, 2016, 44, 9071-82.
- Zhensheng Zhong and Gang Chen,* (News & Views) How RNA Catalyzes Cyclization. Nat Chem Biol, 2015, 11, 830-1.
- Zhensheng Zhong, Lai Huat Soh, Ming Hui Lim, and Gang Chen,* (a special issue dedicated to Singapore's Golden Jubilee) A U·U Pair to U·C Pair Mutation-Induced RNA Native Structure Destabilization and Stretching Force-Induced RNA Misfolding. ChemPlusChem, 2015, 80, 1267-78.
- Gitali Devi, Yuan Zhou, Zhensheng Zhong, Desiree-Faye Kaixin Toh, and Gang Chen,* RNA Triplexes – From Structural Principles to Biological and Biotech Applications. Wiley Interdiscip Rev RNA, 2015, 6, 111-28.
- Xing Ma, Gitali Devi, Qiuyu Qu, Desiree-Faye Kaixin Toh, Gang Chen,* Yanli Zhao,* Intracellular Delivery of Antisense Peptide Nucleic Acid by Fluorescent Mesoporous Silica Nanoparticles, Bioconjugate Chem, 2014, 25, 1412-20.
- Gitali Devi, Zhen Yuan, Yunpeng Lu, Yanli Zhao,* and Gang Chen,* Incorporation of Thio-pseudoisocytosine into Triplex-Forming Peptide Nucleic Acids for Enhanced Recognition of RNA Duplexes. Nucleic Acids Res, 2014, 42, 4008-18.
- Yuan Zhou, Elzbieta Kierzek, Zi Ping Loo, Meraldo Antonio, Yin Hoe Yau, York Wieo Chuah, Susana Geifman-Shochat, Ryszard Kierzek,* and Gang Chen,* Recognition of RNA duplexes by chemically modified triplex-forming oligonucleotides. Nucleic Acids Res, 2013, 41, 6664-73.
- Ignacio Tinoco, Jr.,* Gang Chen, and Xiaohui Qu, (2010) RNA reactions one molecule at a time, in RNA Worlds, (Gesteland, R.F., Cech, T.R., and Atkins, J.F., Eds.), Cold Spring Harbor Laboratory Press. Cold Spring Harb Perspect Biol. doi: 10.1101/cshperspect.a003624
- Gang Chen and Douglas H. Turner,* Consecutive GA pairs stabilize medium-size RNA internal loops. Biochemistry, 2006, 45, 4025-43

Biography:

Dr. Gang CHEN received his B.S. degree in Chemistry at the University of Science and Technology of China (USTC) in 2001. He did his Ph.D. studies with Prof. Douglas TURNER in the Department of Chemistry at the University of Rochester. His Ph.D. work involved thermodynamic and NMR studies of RNA internal loops. A better understanding of the sequence dependence of thermodynamics for RNA structures will improve the accuracy of the RNA secondary structure prediction programs such as MFOLD and RNAstructure. He earned his Ph.D. in 2005. He was a postdoctoral fellow in Prof. Ignacio TINOCO's lab in the Department of Chemistry at the University of California, Berkeley from January 2006 to June 2009. His research in Tinoco lab was on single-molecule mechanical unfolding and folding of RNA pseudoknots by laser optical tweezers, which provided new insights into ribosomal reading-frame regulation by cis-acting mRNA structures. He was a Research Associate in Prof. David MILLAR's lab in the Department of Molecular Biology at The Scripps Research Institute working on HIV-1 Rev-RRE assembly using single-molecule fluorescence techniques. In July 2010, he joined the faculty in the Division of Chemistry and Biological Chemistry at Nanyang Technological University (NTU) in Singapore. At NTU, Dr Gang CHEN has one optical tweezers lab, and one wet lab equipped with facilities for biophysics, molecular biology, and chemical synthesis work (http://www.ntu.edu.sg/home/rnachen/).

TITLE

Selenium Atom-specific Functionalization of Nucleic Acids for Structure and Function Studies

Cen Chen, Jianhua Gan, Wen Zhang, Oksana O. Gerlits, Jozef Salon,
Julianne Caton-Williams, Sibo Jiang, Hehua Liu, and Zhen Huang*, Professor and Director of SeNA Research Laboratory,
Department of Chemistry, Georgia State University, Atlanta, GA 30303, USA; Email: Huang@gsu.edu

Abstract :

There are total five essential elements (H, C, N, O and P) in nucleic acids. Single Se-atom replacement (or atom-specific mutagenesis) of nucleic acids means the substitution of O with Se atom. Atom-specifically functionalized nucleic acids by introducing the sixth element (such as Se) can offer nucleic acids with many unique and novel properties (such as facilitated crystallization and phase determination) without significant perturbation of 3D structures of nucleic acids and their protein complexes. Nucleic acids possess not only the ability to store genetic information and participate in transcription and translation, but also the capacity to adopt well-defined 3D structures, which can be readily adjusted to meet various functional needs (such as catalysis and therapeutics). Although the importance of numerous nucleic acids in catalysis, gene expression, protein binding and therapeutics has been acknowledged by the entire scientific society, current understanding of nucleic acid-protein functions and structures is still limited. Thus, this novel atom-specific mutagenesis provides important tools to investigate nucleic acid structure/folding, recognition and catalysis, to study nucleic acids and their protein interactions, to improve biochemical and biophysical properties of nucleic acids, to facilitate gene silencing and RNA & DNA nanotechnology, and to explore potential nucleic acid therapeutics. Our presentation will focus on the most recent selenium-atom functionalization of nucleic acids and their potential applications in 3D structure-and-function studies and anticancer therapeutics in molecular medicine.

Work is supported by NIH (R01GM095881, GM095086, ES026935) and NSF (MCB-0824837 & CHE-0750235).

Selected Publications:

- Jing Zhang, Hehua Liu, Qingqing Yao, Xiang Yu, Yiqing Chen, R. Cui, B. Wu, L. Zheng, J. Zuo, Zhen Huang*, Jinbiao Ma* and Jianhua Gan*,"Structural basis for single-stranded RNA recognition and cleavage by C3PO", Nucleic Acids Research, 2016, 44, 9494–9504.
- Liqin Zhang, Zunyi Yang, Sefah, Bradley, Hoshika, M.-J. Kim, H.-J. Kim, Zhu, Sena Cansiz, I-Ting Teng, Carole Champanhac, Christopher McLendon, Chen Liu, Wen Zhang, Dietlind L. Gerloff3, Zhen Huang*, Weihong Tan* and Steven A. Benner*, "Crystal Structure, Evolution, and Function of Six-Nucleotide DNA. Exploring its Large Sequence Space", Journal of American Chemical Society, 2015, 137, 6734−6737.
- Rob Abdur, O. Gerlits, Jianhua Gan, J. Jiang, J. Salon, A. Kovalevsky, A. Chumanevich, I. Weber, Zhen Huang*, "Novel Complex MAD Phasing and RNase H Structural Insights by Selenium Oligonucleotides", 2014, Acta Crystallographica Section D, 2014, D70, 354-361.
- Jia Sheng, Jianhua Gan, Alexie Soars, Jozef Salon and Zhen Huang*, "Structural Insights of Non-canonical UU Pair and Hoogsteen Interaction Probed with Se Atom", Nucleic Acids Research, 2013, 41, 10476-10487.
- Huiyan Sun, et. al., Liu, Zhen Huang*, "2-Selenouridine Triphosphate Synthesis and Se-RNA Transcription", RNA, 2013, 19, 1309-1314.
- Jozef Salon, Jianhua Gan, Rob Abdur, Hehua Liu and Zhen Huang*, "Synthesis of 6-Se-Guanosine RNAs for Structural Study", Organic Letter, 2013, 15, 3934-3937.
- Wen Zhang, Abdalla E. Hassan, and Zhen Huang*, "Synthesis of Novel Di-Se-containing Thymidine and Se-DNAs for Structure and Function Studies", Science China: Chemistry, 2013, 56, 273-278.
- 2. Huiyan Sun, Jia Sheng, Abdalla E. A. Hassan, Sibo Jiang, Jianhua Gan and Zhen Huang*, "Novel RNA Base Pair with Higher Specificity using Single Selenium Atom", Nucleic Acids Res., 2012, 40, 5171-5179.
- Jia Sheng, Wen Zhang, Abdalla E. A. Hassan, Jianhua Gan, Alexei Soares, Song Geng, Yi Ren, Zhen Huang*, "Hydrogen Bond Formation between the Naturally Modified Nucleobase and Phosphate Backbone", Nucleic Acids Research, 2012, 40, 8111-8118.
- Wen Zhang, Jia Sheng, Abdalla E. Hassan, and Zhen Huang*, "Synthesis of Novel 2'-Deoxy-5-(Methylselenyl)Cytidine and Se-DNAs for Structure and Function Studies", Chemistry-An Asian Journal, 2012, 7, 476-479.
- Lin, L.; Sheng, J.; Huang, Z. Chemical Society Reviews, 2011, 40, 4591.
- Sheng, J.; Hassan, A. ; Zhang, W.; Zhou, J.; Xu, B.; Soares, A. S.; Huang, Z. Nucleic Acids Res., 2011, 39, 3962.

Biography:

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 W. Szostak (2009 Nobel Laureate in Medicine). 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 currently Professor of Chemistry and Chemical & Structural 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 **(SeNA: selenium nucleic acid; TeNA: tellurium nucleic acid)** 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.

TITLE

The Discovery of a Novel Androgen Receptor for the Treatment of Prostate Cancer

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Abstract:

HC-1119 is a novel androgen receptor antagonist for the treatment of prostate cancer. It is current in phase I clinical trials. We will discuss it's discovery and pre-clinical data.

Selected Publications:

- Jemal A, Siegel R, Xu J, et al. Cancer statistics, 2010. CA Cancer J Clin 2010, 60(2):277–300.
- Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin 2012, 62(1): 10-29.
- Huggins C, Hodges C V. Studies on prostatic cancer: I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. The Journal of urology 2002, 167(2): 948-951.
- Mills I G. Maintaining and reprogramming genomic androgen receptor activity in prostate cancer. Nat Rev Cancer, 2014, 14(3): 187-198.
- Clegg N J, Wongvipat J, Joseph J D, et al. ARN-509: a novel antiandrogen for prostate cancer treatment. Cancer Res, 2012, 72(6): 1494-1503.

Biography:

Dr. Yuanwei Chen,
CEO and Founder of Hinova Pharmaceuticals Inc.
Prof. of Sichuan University
President of Chengdu High-Tech Talent Promotion Association

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).

TITLE

Cyclic-di-AMP Exhibits Distinct Binding Mode to Cyclic-di-GMP in Exhibiting Different Roles in Bacterial Pathogenicity

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Abstract:

Big nucleic acid molecules, such as ncRNA or miRNA, have been found to play important roles in a variety of biological functions in eukaryotic cells. Our group is, on contrast, interested in studying very small RNA molecules and their roles in causing bacterial pathogenicity. Cyclic di-nucleotides, such as c-di-GMP, c-di-AMP, or cGAMP, which are comprised two nucleotides that are mutually cyclized, have emerged as important second messengers in bacterial signal transduction and pathogenicity. A rapidly expanding body of work has described the multiple biological functions mediated by c-di-GMP and c-di-AMP in bacteria, as well as their actions as activators for the STING protein of the mammalian innate immune response. Quite a few of c-di-GMP-bound structures have been reported, which reveal the unique binding modes of c-di-GMP and how c-di-GMP exerts its action in bacterial signal transduction and regulation (For the most recent account, see the review by Chou and Galperin **(J. Bacteriology, 2016)**. However, comparatively fewer structures of complexes between c-di-AMP and its receptors or effectors are available. Here we report the biophysical and structural studies of c-di-AMP in complex with a bacterial cation−proton antiporter (CpaA) RCK (regulator of the conductance of K+) protein from Staphylococcus aureus (Sa). The crystal structure of the SaCpaA_RCK C-terminal domain (CTD) in complex with c-di-AMP was determined to a resolution of 1.81 Å. This structure revealed two well-liganded water molecules, each interacting with one of the adenine bases by a unique H2Olp−π interaction to stabilize the complex. Sequence blasting using the SaCpaA_RCK primary sequence against the bacterial genome database returned many CpaA analogues, and alignment of these sequences revealed that the active site residues are all well-conserved, indicating a universal c-di-AMP binding mode for CpaA_RCK. A proteoliposome activity assay using the full-length SaCpaA membrane protein indicated that c-di-AMP binding alters its antiporter activity by approximately 40%. A comparison of this structure to all other reported c-di-AMP−receptor complex structures revealed that c-di-AMP binds to receptors in either a “U-shape” or “V-shape” mode. The two adenine rings are stabilized in the inner interaction zone by a variety of CH−π, cation−π, backbone−π, or H2Olp−π interaction, but more commonly in the outer interaction zone by hydrophobic CH−π or π−π interaction. This structure provides an understanding of the mechanism of how c-di-AMP binds receptor proteins in a special way different to that of c-di-GMP.

Work is supported by the Ministry of Education, Taiwan, under the ATU plan, and by the National Science Council, Taiwan (grants 102-2113-M-005-006-MY3)

Selected Publications:

◆ Shan-Ho Chou* & Michael Y. Galperin* (2016) (Review article) Diversity of c-di-GMP-binding proteins and mechanisms, J. Bacteriology, 198 (1), 1-15

◆ Yuan-Chao Lou, Tsai-Hsuan Weng, Yi-Chuan Li, Yi-Fen Kao, Shan-Ho Chou, Chwan-Deng Hsiao and Chinpan Chen⁎? (2015) Structure and dynamics of the polymyxin-resistance-associated response regulator PmrA in complex with the promoter DNA, Nature Communications, 6:8838

◆ Qing Tang, Hong-Liang Qian, You-Wen Zhao, Kang Yin, Xun Wang, Wen Wang, Shan-Ho Chou, Jin He*, (2016) Cyclic di-GMP contributes to adaption and virulence of Bacillus thuringiensis through a riboswitch-regulated collagen adhesion protein, Scientific Reports, 6, 28807

◆ Hang Zhou, Cao Zheng, Jianmei Su, Bo Chen, Yang Fu, Yuqun Xie, Qing Tang, Shan-Ho Chou, Jin He*, (2016) Characterization of a natural triple tandem c-di-GMP riboswitch and application of the riboswitch-based dual-fluorescence reporter, Scientific Reports, 6, 20871

◆ Jianmei Su, Xia Zou, Liangbo Huang, Tenglong Bai, Meng Yuan, Shan-Ho Chou, Ya-Wen He, Haihong Wang, Jin He*, (2016) DgcA, a diguanylate cyclase from Xanthomonas oryzae pv. oryzae regulates bacterial pathogenicity on rice. Scientific Reports, 6, 25978

◆ Ya-Wen He* and Shan-Ho Chou*, (2015) Cyclic di-GMP regulation in plant-pathogenic bacteria, In Virulence Mechanisms of Plant-Pathogenic Bacteria (Chapter 6) (Wang, N., Jones, J. B., Sundin, G. W., White, F. F., Hogenhout, S. A., Poper, C., Fuente, L. D. L., and Ham, J. H., Eds.), pp 107-124, APS PRESS, St. Paul, Minnesota U.S.A.

◆ Ko-Hsin Chin, Juin-Ming Liang, Jauo-Guey Yang, Min-Shao Shih, Zhi-Le Tu, Yu-Chuang Wang, Xing-Han Sun, Nien-Jen Hu, Zhao-Xun Liang, J Maxwell Dow, Robert P Ryan, Shan-Ho Chou* (2015) Structural insights into the distinct binding mode of cyclic di-AMP with SaCpaA-RCK, Biochemistry, 54, 4936−4951.

◆ Yuan-Chao Lou, Tsai-Hsuan Weng, Yi-Chuan Li, Yi-Fen Kao, Shan-Ho Chou, Chwan-Deng Hsiao and Chinpan Chen⁎?, (2015) Structure and dynamics of the polymyxin-resistance-associated response regulator PmrA in complex with the promoter DNA, Nature Communications, 6:8838

Biography:

Dr. Shan-Ho Chou is currently a chair professor of the Institute of Biochemistry, National Chung Hsing University, Taiwan. He received his bachelor's degree in chemistry from the National Taiwan Normal University, a master degree in biochemistry from the National Taiwan University, and a Ph.D. in chemistry from the University of Washington in Seattle, WA. At the first stage of his research career, he studied unusual nucleic acid structures by using nuclear magnetic resonance (NMR) analysis and found quite a few of stable nucleic acid structures different from the WC base-paired duplex, for which he was invited to write several review papers in the journals of **Trends in Biochemical Science, Nucleic Acids Research and the Journal of Molecular Biology**. In his second stage, he switched to studying structural genomics of the plant pathogen X. campestris by X-ray crystallography and solved several important c-di-GMP–protein complex structures, which were published in the **Nucleic Acid Research** and **Nature Communications**. Again, he was invited to write a review paper regarding the interaction principles between c-di-GMP and its receptor proteins from published complex structures in the **Journal of Bacteriology, 2016**. In the current stage, he is now combining X-ray, NMR, and single-particle cryo-EM techniques to study multi-domain proteins and complexes associated with c-di-GMP or c-di-AMP binding as well as with some unique natural product synthesis. Since cyclic-dinucleotides have been found to play so many important roles in controlling bacterial physiology such as biofilm formation, virulence factor secretion, cell wall synthesis, potassium ion transportation etc. as well as their interactions with environment, there is no doubt that this field is going to dominate the bacterial research for a long time to come. His research has been funded by the Ministry of Education and the Ministry of Science and Technology from Taiwan. He is an author of more than 100 research papers, reviews, and book chapters, and has received many prestigious awards from Taiwan, for examples, the outstanding awards twice in the Chemistry and Biology from the Ministry of Science and Technology.

TITLE

Photomodulating the Functions of Nucleic Acids/Protein Complexes with Caged Oligonucleotides

Yuzhuo Ji, Jiali Yang, Lijia Yu, Jinhao Zhang, Li Wu, Yuan Wang and Xinjing Tang*,
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Abstract :

Chemical approaches for controlling biomolecular functions have become increasingly important in biological and biomedical research. Photolabile groups (photocages) represent one of most effective approaches to achieve high spatiotemporal resolution with light activation. It has been successfully used to cage many functional oligonucleotides to photomodulate gene expression in vitro and in vivo, such as ribozymes, DNAzymes, complementary RNA or DNA oligonucleotides and their analogs during mRNA transcription, processing, ribosomal binding and translation, and nucleic acid/protein interactions. Previously, possible strategies to modulate gene expression was applied by light activation through either introduction of multiple caging groups on functional nucleic acids to inhibit their interaction with targets or application of inhibitory oligonucleotide strand to temporarily block the interaction. Both strategies have their limitations, such as uncomplete uncaging or side effect of inhibitory strand. By rational design of specific single caged oligonucleotides based on the interaction of nucleic acids/protein, we developed a series of caged antisense oligonucletides and siRNAs. This single caging moiety on caged nucleic acids was supposed to influence the interaction of nucleic acids/proteins and/or their further biological functions. Our presentation will focus on the development of caged antisense oligonucleotides with circular structures and caged siRNA with site-specific modification of single phosphate group, their photomodulation of their interactions with target, and their further gene silencing activities.

This work is supported by National Natural Science Foundation of China (Grant Nos. 21422201and 21372018), the 973 Program (Grant Nos. 2012CB720600, 2013CB933800), and the Program for New Century Excellent Talents in University (Grant No. NCET-10-0203)

Selected Publications:

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- Xiuxian Chen, Qingqing Jin, Lizhu Wu, ChenHo Tung, Xinjing Tang*, Angew Chem. Int. Ed., 2014, 53, 12542-12547
- Li Wu, Yuan Wang, Junzhou Wu, Jie Wang, Xinjing Tang* Nucleic Acids Res., 2013, 41. 677-686
- Yuan Wang, Li Wu, Peng Wang, Cong Lv, Zhenjun Yang and Xinjing Tang* Nucleic Acids Res., 2012, 40, 11155-11162.
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- Pengfei Li, Hongyan He, Zhixuan Wang, Mengke Feng, Hongwei Jin, Yun Wu, Liangren Zhang and Lihe Zhang, Xinjing Tang, Anal. Chem., 2016, 88, 883-889
- Gülnur Imincan, Fen Pei, Lijia Yu, Hongwei Jin, Liangren Zhang, Xiaoda Yang, Lihe Zhang, XinJing Tang*, Anal. Chem., 2016, 88, 4448–4455
- Zhisheng Wu, Duanwei Liang and Xinjing Tang*, Anal Chem., 2016, 88(18), 9213–9218
- Junzhou Wu, Duanwei Liang, Qingqing Jin, Jie Liu, Meiling Zheng Xuanming Duan, and Xinjing Tang*, Chem. Eur. J., 2015, 21,12914-12918.
- Li Wu, Fen Pei, Jinhao Zhang, Junzhou Wu, Mengke Feng, Yuan Wang, Hongwei Jin, Liangren Zhang, Xinjing Tang* Chem. Eur. J., 2014, 20, 12114-12122

Biography:

Prof. Xinjing Tang (Ph.D.) was born in 1976 and raised in Anhui, China. He received his B.S. degree from Shandong University in 1997, and Ph.D. degree from Technical Institute of Physics and Chemistry, the Chinese Academy of Sciences in 2002 (under the supervision of Professor ChenHo Tung, academician of CAS). In 2003, he joined the Department of Chemistry at University of Pennsylvania as a postdoctoral fellow and then as a research associate in laboratory of Professor Ivan J. Dmochowski. He then came back to China and joined State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University. He has received several awards, including Youth Yangtze river scholar of Ministry of Education (2015), awardee of Outstanding Youth Fund of NSFC (2014), Servier Young Investigator Awards in Medicinal Chemistry (2013), New Century Excellent Talents of Ministry of Education (2010), and Luye Award for Distinguished Young Scientist. His current research interests include 1) Photolabile oligonucleotides for regulating nucleic acid functions; 2) Novel fluorescent oligonucleotide probes for sensing the interaction of DNA/RNA and nucleic acids/protein; 3) Cancer early detection with nucleic acid functionalized nanomaterials; 4) Synthesis of analogs of nucleosides and nucleotides. His research has been funded by MOST (973 program), NSFC, MOE et al. He has one US and four Chinese patents, and several Chinese patents are pending.

TITLE

mRNA processing, decay and quality control in eukaryotes

Liang Tong*, William R. Kenan, Jr. Professor and Department Chair, Department of Biological Sciences, Columbia University, New York, NY 10027, USA; Email: ltong@columbia.edu

Abstract:

Most eukaryotic mRNA precursors (pre-mRNAs) must undergo extensive processing, which includes 5 ¢ -end capping, splicing and 3 ¢ -end cleavage and polyadenylation. Replication-dependent histone pre-mRNAs contain a conserved stem-loop structure near the 3 ¢ -end, which is recognized by stem-loop binding protein (SLBP) and the 3 ¢ -5 ¢ exoribonuclease 3 ¢ hExo. Our recent structures of the SLBP-3 ¢ hExo-stem-loop RNA (26 nucleotides) ternary complex have defined the molecular basis for this specific recognition as well as the catalysis by 3 ¢ hExo. Our studies have also revealed how phosphorylation of SLBP regulates this recognition.

mRNA decay is controlled by sequence elements in the RNA as well as decapping/deadenylation machineries. Our studies have revealed the molecular basis for the recognition of the constitutive decay element (CDE) by the ROQ domain of Roquin. Roquin has a central role in repressing autoimmunity, and mice deficient in both Roquin and Roquin-2 in T cells or carrying a single-point mutation in the ROQ domain (M199R, sanroque mutation) exhibit a lupus-like autoimmune phenotype.

mRNA 5 ¢ -end capping occurs early during transcription and it was generally believed that the capping process is always successful and no quality control mechanism was known. Our studies have shown that yeast Rai1 and its mammalian homolog DXO are central players in a novel RNA quality surveillance pathway, promoting the degradation of RNAs with incomplete 5 ¢ -end capping. Structures of Rai1 and DXO in complex with various RNA substrates have revealed novel mechanisms for the diverse activity profiles of these enzymes. Overall, these results have opened up a new area of research in RNA biology.

This work is supported by NIH (R35GM118093).

Selected Publications:

◆ V.Y.F. Wang, X. Jiao, M. Kiledjian & L. Tong. (2015). Structural and biochemical studies of the distinct activity profiles of Rai1 proteins.

Nucl. Acids Res. 43, 6596-6606.

◆ D. Tan, M. Zhou, M. Kiledjian & L. Tong. (2014). The ROQ domain of Roquin recognizes mRNA constitutive-decay element and

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Acad. Sci. USA, 111, 13834-13839.

◆ J. Zhang, D. Tan, E.F. DeRose, L. Perera, Z. Dominski, W.F. Marzluff,* L. Tong* & T.M. Tanaka Hall.* (2014). Molecular mechanisms for the regulation of histone mRNA stem-loop-binding protein by phosphorylation. Proc. Natl. Acad. Sci. USA, 111, E2937-E2946.

(*–co-corresponding authors)

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◆ X. Jiao,* J.H. Chang,* T. Kilic, L. Tong$ & M. Kiledjian.$ (2013). A mammalian pre-mRNA 5´ end capping quality control mechanism and an unexpected link of capping to pre-mRNA processing. Mol. Cell, 50, 104-115. (*–equal first authors, $–co-corresponding authors) (Preview by J.S. Mugridge & J.D. Gross, 2-4)

◆ K. Xiang, J.L. Manley & L. Tong. (2012). An unexpected binding mode for a Pol II CTD peptide phosphorylated at Ser7 in the active site of the CTD phosphatase Ssu72. Genes Develop. 26, 2265-2270.

◆ J.H. Chang,* X. Jiao,* K. Chiba, C.-S. Oh, C.E. Martin, M. Kiledjian$ & L. Tong.$ (2012). Dxo1 is a new type of eukaryotic enzyme with both decapping and 5'-3' exoribonuclease activities. Nature Struct. Mol. Biol. 19, 1011-1017. (*–equal first authors, $–co-corresponding authors) (Research Highlight in Nature Chem. Biol. Nov. 2012)

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◆ K. Xiang, T. Nagaike,* S. Xiang,* T. Kilic, M.M. Beh, J.L. Manley & L. Tong. (2010). Crystal structure of the human symplekin-Ssu72-CTD phosphopeptide complex. Nature, 467, 729-733. (*–equal second authors)

◆ X. Jiao, S. Xiang, C.-S. Oh, C.E. Martin, L. Tong & M. Kiledjian. (2010). Identification of a quality-control mechanism for eukaryotic mRNA 5'-end capping. Nature, 467, 608-611.

◆ S. Xiang, A. Cooper-Morgan, X. Jiao, M. Kiledjian, J.L. Manley & L. Tong. (2009). Structure and function of the 5'®3' exoribonuclease Rat1 and its activating partner Rai1. Nature, 458, 784-788.

Biography:

Prof. Liang Tong (Ph.D.) was born and raised in Dalian, China. He received his B.Sc. degree from Peking University (under the supervision of Professor You-Qi Tang), and Ph.D. degree from University of California, Berkeley in 1989 (under the supervision of Professor Sung-Hou Kim). He was a post-doctoral fellow with Prof. Michael Rossmann at Purdue University from 1989 to 1992. He was then recruited as a Senior Scientist to Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT, where he established the first protein crystallography/structure-based drug design laboratory in the company, and was promoted to Principal Scientist in 1996. He received the Vice President's Golden Achievement Award in 1996, and then the first Boehringer Ingelheim Worldwide Research and Development Award in 1997. He joined the faculty at the Department of Biological Sciences, Columbia University as an Associate Professor in 1997, and became full Professor in 2004, the Chair of the Department in 2013, and the William R. Kenan, Jr. Professor in 2015. He established a vigorous research program in structural biology at Columbia, funded by federal agencies (NIH and NSF) and industry sources. He has made fundamental contributions to understanding the molecular mechanisms of many biological processes, and has especially distinguished himself in two important areas of biology—metabolic enzymes and proteins involved in mRNA processing and recognition, which is also evidenced by his excellent publication record in these areas, with many papers in journals of the highest impact (Nature, Science and Cell), out of a total of more than 250 publications. He was elected a fellow of the American Association for the Advancement of Science in 2009.

TITLE

A General, Modular Strategy for Small Molecule – RNA recognition

Thomas A. Hilimire, Viktoriya Anokhina, Ryan P. Bennett, Jeffrey M. Chamberlain,
Oliver Swart, John D. McAnany, Harold C. Smith, Stephen Dewhurst, and **Benjamin L. Miller*,**
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Abstract:

Sequence-selective RNA recognition represents an outstanding unsolved problem for the field of Bioorganic Chemistry. In contrast to DNA, there are no heuristics that can map an RNA sequence to a synthetic compound that binds only that sequence. Because of the ever-increasing pace of discovery of RNAs with relevance to basic biology and disease, it has become clear that the development of general methods for the generation of bioactive RNA-binding compounds is a critical need.

We have developed Resin-Bound Dynamic Combinatorial Chemistry (RBDCC) as a method for addressing this challenge. RBDCC allows the rapid in situ synthesis and screening of large (>11,000-compound) libraries in a single test tube without the analytical challenges of “traditional” solution-phase dynamic combinatorial libraries. Using the structure of naturally occurring bisintercalating peptide antibiotics as a starting point, we have applied the RBDCC concept to several RNA targets, including one critical to the life cycle of HIV, and another believed to be responsible for Type I Myotonic Dystrophy. This lecture will discuss the development of RBDCC, its use as an enabling tool for identifying sequence-selective RNA binders, and the further development of RBDCC-discovered compounds as lead molecules with target-relevant activity in vitro and in vivo. We will particularly focus on the development of compounds able to alter -1 ribosomal frameshifting (recoding) in HIV, thereby inhibiting viral replication. As protein recoding is a widely used regulatory mechanism in viruses, bacteria, and eukaryotes (including humans), this strategy may have broad utility. Finally, recent work centered on the identification of small molecules able to interfere with the production of micro RNAs relevant to cancer will be discussed.

Work is supported by NIH (R01 GM100788); Institutional Ruth L. Kirschstein National Research Service Awards GM068411 and AI049815 (T.A.H., J. D. M.), and via the University of Rochester Center for AIDS Research (CFAR), an NIH-funded program (P30 AI078498).

Selected Publications:

◆ McAnany, J. D.; Reichert, J. P.; Miller, B. L. “Probing the geometric constraints of RNA binding via dynamic combinatorial chemistry” Bioorg. Med. Chem., 2016, 24, 3940-3946.

◆ Hilimire, T. A.; Bennett, R. P.; Stewart, R. A.; Garcia-Miranda, P.; Blume, A.; Becker, J.; Sherer, N.; Helms, E. D.; Butcher, S. E.; Smith, H. C.; Miller, B. L. "N-Methylation as a Strategy for Enhancing the Affinity and Selectivity of RNA-binding Peptides: Application to the HIV-1 Frameshift-Stimulating RNA", ACS Chem. Biol., 2016, 11, 88-94.

◆ Carter, J. A.; Triplett, E. J.; Striemer, C. C.; Miller, B. L. “Label-Free, Multiplex Competitive Assay for Small Molecule Pollutants”, Biosens. Bioelectron., 2016, 77, 1-6.

◆ Miller, B. L. “A patch for a splice” Nature Chem. Biol. (News & Views), 2015, 11, 454-455.

◆ Hoskins, J. W.; Ofori, L. O.; Chen, C. Z.; Kumar, A.; Sobczak, K.; Nakamori, M.; Southall, N.; Patnaik, S.; Marugan, J. J.; Zheng, W.; Austin, C. P.; Disney, M. D.; Miller, B. L.; Thornton, C. A. “Lomofungin and dilomofungin: inhibitors of MBNL1-CUG RNA binding with distinct sequence selectivities and cellular effects”, Nucl. Acids Res. 2014, 42, 6591-6602.

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◆ Ofori, L. O.; Hoskins, J.; Nakamori, M.; Thornton, C. A.; Miller, B. L. “From Dynamic Combinatorial “Hit” to Lead: In vitro and in vivo activity of compounds targeting the pathogenic RNAs that cause myotonic dystrophy” Nucl. Acids Res., 2012, 40, 6380-6390.

◆ Deane, R.; Singh, I.; Sagare, A. P.; Bell, R. D.; Ross, N. T.; LaRue, B.; Love, R.; Perry, S.; Paquette, N.; Deane, R. J.; Meenakshisundaram, T.; Zarcone, T.; Friedman, A. E.; Miller, B. L.; Zlokovic, B. V. “A novel multi-modal RAGE inhibitor controls Abeta-mediated brain disorder in mice” J. Clin. Invest., 2012, 122, 1377-1392.

◆ Palde, P. B.; Ofori, L. O.; Gareiss, P. C.; Lerea, J.; Miller, B. L. “Strategies for Recognition of Stem-loop RNA Structures by Synthetic Ligands: Application to the HIV-1 Frameshift Stimulatory Sequence”, J. Med. Chem. 2010, 53, 6018-6027.

◆ Wender, P. A.; Miller, B. L. “Synthesis at the Molecular Frontier” Nature 2009, 460, 197-201.

◆ Gareiss, P. C.; Sobczak, K.; McNaughton, B. R.; Palde, P. B.; Thornton, C. A.; Miller, B. L. “Dynamic Combinatorial Selection of Small Molecules Capable of Inhibiting the (CUG) Repeat RNA – MBNL1 Interaction in vitro: Discovery of Lead Compounds Targeting Myotonic Dystrophy (DM1)” J. Am. Chem. Soc., 2008, 130, 16254-16261.

◆ McNaughton, B. R.; Gareiss, P. C.; Miller, B. L. "Identification of a Selective Small-Molecule Ligand for HIV-1 Frameshift-Inducing Stem-Loop RNA from an 11,325 Member Resin Bound Dynamic Combinatorial Library" J. Am. Chem. Soc., 2007, 129, 11306-11307.

Biography:

Prof. Benjamin L. Miller completed his undergraduate studies at Miami University (Ohio), receiving degrees in Chemistry (B.S.), Mathematics (A.B.), and German (A.B.) in 1988. He next moved to Stanford University, where he carried out his Ph. D. research in Chemistry under the direction of Paul Wender. Following a stint as an NIH postdoctoral fellow at Harvard in Stuart Schreiber's laboratory, he joined the University of Rochester faculty in 1996. His group's expertise in molecular recognition, combinatorial chemistry, nanotechnology, and optical sensing has been applied to the development of novel optical biosensor platforms and synthetic compounds targeting several human diseases. He is currently Professor of Dermatology, Biochemistry and Biophysics, Biomedical Engineering, and Optics, as well as a member of the graduate programs in Chemistry, Physics, and Materials Science. The Miller group's research has been recognized with the Camille Dreyfus Teacher-Scholar Award (2001-2006), the Rochester Business Journal Health Care Achievement Award (2009), and the Future of Health Technology Award (2010). He is a past Chair of the Instruments and Systems Development (ISD) Study Section at the National Institutes of Health (2014-2016), and is a frequent ad-hoc Chair of NIH review SBIR review panels in Biochemistry, Biophysics, and Drug Discovery. Miller has published over 130 peer-reviewed papers, and has served as the editor of a book covering the field of Dynamic Combinatorial Chemistry (Wiley, 2009). Miller's work has resulted in over 20 issued U. S. and international patents, with many more pending. As an entrepreneur, Miller is a founder of Adarza BioSystems, Inc., a multiplex optical biodetection company located in Rochester, NY and St. Louis, MO. He is also the Academic Lead for the Integrated Photonic Sensors working group in AIM Photonics.

TITLE

Non-Canonical G-quadruplexes Trigger hCEB1 Minisatellite Instability in Saccharomyces cerevisiae

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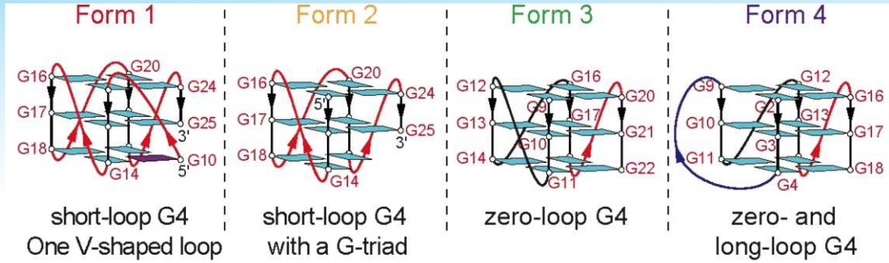
Abstract:

G-quadruplexes (G4) are polymorphic four-stranded structures formed by certain G-rich nucleic acids, with various biological functions. However, sequence and structural features dictating their formation and function in vivo are still poorly understood, especially most dramatically for complex G-rich sequences where guanine contiguity may promote the formation of multiple and non-canonical G4s. We previously defined rules leading to G4-induced genomic instability in yeast using the monomorphic hCEB25-G4 upon stabilization with the Phen-DC3 G4-stabuilizing ligand Phen-DC3 or in the absence of the G4-unwinding helicase Pif1. Here we report a structure-function mutational analysis of the non-canonical complex hCEB1 G4-forming sequence (TGGGCTGAGGGGGGAGGGAGGGTGGCCTGCGGAGGTCCC). The combination of a nearby G-doublet, three G-triplets and a G-sextet within 24 nucleotides allow the formation of four G4-prone motifs that form alternative G4 conformations. Biophysical analyses show that Form 1 adopts a short loop G4 including a V-shaped loop; Form 2 contains a (4n-1) guanines tetrad core allowing the formation of a short loop G-triad; Form 3 bears a zero-nucleotide loop; and Form 4 is a heterogeneous zero-nucleotide loop-bearing monomer or an interlocked dimer. In vivo, approximately two third of the instability was imputable to Form 1 and 2 but differentially in the presence of Phen-DC3 or in the absence of Pif1. Forms 3 and likely other(s) contribute to the remaining instability. Altogether, this work demonstrates the existence of non-canonical G4 in cells, thus broadening the definition of G4 motifs. The absence of competition between forms in vivo further suggests that G4 formation is the limiting step in inducing genomic stability.



Selected Publications:

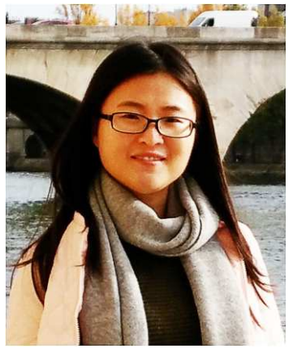
◆ Xiaojie Cui, Qiang Zhang, Han Chen, Jiang Zhou, and Gu Yuan*, "ESI Mass Spectrometric Exploration of Selective Recognition of G-Quadruplex in c-myb Oncogene Promoter Using a Novel Flexible Cyclic Polyamide", J. Am. Soc. Mass Spectrom., 2014, 25, 684.

◆ Xiaojie Cui, Sen Lin, Jiang Zhou and Gu Yuan*, "Investigation of non-covalent interaction of natural flexible cyclic molecules with telomeric RNA G-quadruplexes by electrospray ionization mass spectrometry", Rapid Commun. Mass Spectrom., 2012, 26 , 1803.

◆ Xiaojie Cui, Sen Lin and Gu Yuan*, "Spectroscopic probing of recognition of the G-quadruplex in c-kit promoter by small-molecule natural products", Int. J. Biol. Macromol., 2012, 50, 996.

◆ Qiang Zhang, Xiaojie Cui, Sen Lin, Jiang Zhou, and Gu Yuan*, "Convenient Method for the Synthesis of a Flexible Cyclic Polyamide for Selective Targeting of c-myb G-quadruplex DNA", Org. Lett., 2012, 14, 6126.

◆ Xiaojie Cui and Gu Yuan*, "Formation and recognition of G-quadruplex in promoter of c-myb oncogene by electrospray



Biography:

Dr. Xiaojie Cui received her B. S. degree from Shandong University in 2009, and Ph. D. from Peking University in 2014 under the supervision of Professor Gu Yuan. She stayed in Yuan's lab as an assistant researcher for one year studying the interactions between small molecule ligands and DNA higher-order structures such as G-quadruplexes mainly by ESI Mass Spectrometry. In 2015, she joined Institute Curie in Paris, France as a Post-doctoral fellow in the team of Dr. Alain Nicolas (CNRS Research Director). Since then, she has been working on the replication-recombination dependent genomic instabilities triggered by G-quadruplexes using yeast Saccharomyces cerevisiae as a model system. Her current work focuses on the single-strand DNA accumulation during replication induced by G-quadruplex obstacles.

TITLE

In vitro Selection of New Metal-Specific RNA-cleaving Deoxyribozymes

Po-Jung Jimmy Huang, Wenhu Zhou, Runjhun Saran, Mahsa Vazin, Lingzi Ma, and **Juewen Liu***,
Professor, Department of Chemistry, University of Waterloo,
Waterloo, Ontario, N2L 3G1, Canada; Email: Huang@gsu.edu

Abstract :

The DNA counterpart of ribozymes is called deoxyribozymes or DNAzymes. DNAzymes are DNA-based catalysts, and they are highly attractive for biosensor development, viral/cancer RNA cleavage, and nanotechnology. At the same time, they are excellent biochemical model systems. In the last few years, my lab at the University of Waterloo isolated a suite of new RNA-cleaving DNAzymes that are highly specific for various transition metal ions as well as physiologically important metal ions. Our work started with a series of new lanthanide-dependent DNAzymes, displaying intriguing metal binding properties. A phosphorothioate (PS) modification refers to the substitution of one of the non-bridging phosphate oxygen atoms in nucleic acids by sulfur. We also developed PS-modified DNAzymes for recruiting thiophilic metals such as Cd2+ and Cu2+. Direct selection of a highly active DNAzymes using Ag+ was also achieved, and this study has increased our mechanistic understanding of the RNA cleavage reaction. Finally, we obtained Na+- and Ca2+-specific DNAzymes, and showed biochemical evidence of a Na+-binding aptamer. Most of these DNAzymes were made into fluorescent biosensors for metal ions down to low parts-per-billion concentrations.

Work is supported by NSERC and CIHR of Canada.

Selected Publications:

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- Zhou, W.; Saran, R.; Chen, Q.; Ding, J.; Liu, J., A New Na+-Dependent RNA-Cleaving DNAzyme with over 1000-Fold Rate Acceleration by Ethanol. ChemBioChem 2016, 17, 159-163.
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- Huang, P.-J. J.; Vazin, M.; Liu, J., Desulfurization Activated Phosphorothioate DNAzyme for the Detection of Thallium. Anal. Chem. 2015, 87, 10443-10449
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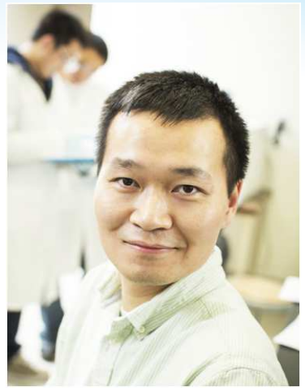

Biography:

Prof. Juewen Liu (Ph.D.) was born in 1978 and raised in Changsha, Hunan, China. He received his B.S. degree from the University of Science & Technology of China (USTC) in 2000 (under the supervision of Professor Yitai Qian), and Ph.D. degree from the University of Illinoi s at Urbana-Champaign in 2005 (under the supervision of Professor Yi Lu). After a postdoctoral research with Professor C. Jeffrey Brinker at Sandia National Labs and the University of New Mexico, he joined the Department of Chemistry at the University of Waterloo as assistant professor and was later promoted to associate professor with tenure in 2014. He is also affiliated with the Waterloo Institute for Nanotechnology (WIN). He has received several awards, including the Fred Beamish Award from the Canadian Society for Chemistry in 2014 for his contribution in bioanalytical chemistry and an Ontario Early Researcher Award in 2011. He is very active in community services: he serves as an Associate Editor for Analytical Methods (an RSC journal), on the editorial board of Journal of Analysis and Testing (Springer) and on the editorial advisory board of Langmuir. He is an expert on functional nucleic acids chemistry, in vitro selection, bioanalytical chemistry, and biointerface chemistry. Some of the current projects in his lab include in vitro selection of new RNA-cleaving DNAzymes for metal detection and in vivo RNA cleavage, selection of aptamers, liposome-based hybrid materials and liposome/nanomaterials interaction, and molecularly imprinted polymers. The long term goal of the Liu lab is to develop molecular tools and materials for understanding and solving environmental and biomedical problems. Since 2002, he has published over 170 papers, receiving over 10,000 citations. About 30 of his papers have been cited over 100 times. He is also a co-inventor of about 15 patents. His lab received funding from various Canadian granting agencies including NSERC, CFI and CIHR in Canada.

TITLE

Aptamer Functionalized Microfluidic Device for Synergistic Enrichment of Circulating Tumor Cells

Chaoyong Yang
Department of Chemical Biology, College of Chemistry and Chemical Engineering, Xiamen University, China. Email: cyyang@xmu.edu.cn

Abstract:

Circulating Tumor Cells (CTCs) have been demonstrated to be excellent biomarkers for cancer diagnosis and prognosis. During the past ten years, tremendous amounts of effort have been invested in developing various microfluidic platforms based on different separation principles ranging from sized/deformity oriented techniques to immunocapture methods for CTC enrichment. Unfortunately, most of these platforms are often limited by a capture performance tradeoff between high efficiency and high purity. Towards solving such inherent interest of attaining high throughput, capture efficiency and purity, we have designed a hybrid microfluidic device for the enrichment of CTCs relying on both size-based separation and aptamer affinity capturing principles. Our computationally optimized and aptamer functionalized micropillar array chip allows separation of target cells from non-target cells based on size while facilitating cell-micropillars collision hence highly efficient affinity capturing of CTCs. In this talk, new progress on aptamer selection and characterization will be reported, the design, optimization, and performance of the integrated device will be presented.

Work is supported by NSFC (21325522, 21422506, 21435004, 21275122).

Selected Publications:

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- Song, Y; Tian, T; Shi, Y; Liu, W; Zou, Y, Khajavand, T; Zhu, Z; Yang, C*. Enrichment and Single-Cell Analysis of Circulating Tumor Cells, Chem. Sci., 2017,8, 1736-1751
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- Zhu Z; Guan, Z; Jia S; Lei Z; Lin, S; Zhang, H; Ma, Y; Tian, Z; Yang, C*; Au@Pt Nanoparticle Encapsulated Target-responsive Hydrogel with Volumetric Bar-chart Chip Readout for Quantitative Point-of-care Testing, Angew. Chem. Int. Ed., 2014, 53, 12503-12507
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- Zhu, Z; Song, Y; Li, C; Zou, Y; Zhu, L; An, Y; Yang, C*. Monoclonal Surface Display SELEX for Simple, Rapid, Efficient and Cost-Effective Aptamer Enrichment and Identification, Anal Chem, 2014, 86, 5881-5888
- Tan, J; Ding, L; Ju, H*; Yang, Y; Li, X; Shen, Z; Zhu, Z; Yu, J*; Yang, C*; A Multifunctional Nanomicelle for Real-Time Targeted Imaging and Precise Near-Infrared Therapy of Cancer, Angew. Chem. Int. Ed., 2014, 53, 9544-9549

Biography:

Prof. Chaoyong Yang received his PhD from University of Florida in 2006 under the guidance of Professor Weihong Tan in August 2006. After graduation, he moved to University of California, Berkeley for postdoctoral training in Professor Richard Mathies' group. In 2008, he joined the faculty of the Department of Chemical Biology at Xiamen University where he is now the Lu Jiaxi Professor and vice-chair. Professor Yang has published over 130 articles in international journals which have received over 5000 citations, and is named inventor on over 20 patent applications. He sits on the Advisor Boards of Analytical Chemistry, Analyst, and Biomicrofluidics. He serves as associate editor for BMC Biochemistry and is an Editorial Board Member of Scientific Reports. He is the recipient of CAPA Distinguished Faculty Award in 2012, National Outstanding Young Investigator Award in 2013, Chinese Young Analyst Award in 2015, and Chinese Chemical Society-Royal Society of Chemistry Young Chemist Award in 2016. His current research is particularly focused on bio-sensing, microfluidics, and high throughput evolution.

TITLE

The Roles of DNA Mini-dumbbell in Repeat Expansions

Pei Guo and **Sik Lok Lam***, Associate Professor, Department of Chemistry,
The Chinese University of Hong Kong, Shatin, New Territories,
Hong Kong; E-mail: lams@cuhk.edu.hk

Abstract:

Expansions of TTTA and CCTG repeats are associated with the formation of a protective biofilm in Staphylococcus aureus and myotonic dystrophy type 2 in human, respectively. Recently, we have reported a novel mini-dumbbell (MDB) structure formed by two CCTG or TTTA repeats. These MDBs are formed by two regular type II tetraloops which have a distinctive folding geometry. Specifically, the first and fourth loop residues form the loop-closing base pair. The second loop residue is positioned in the minor groove whereas the third loop residue stacks on the loop-closing base pair. More importantly, there are multiple stabilizing loop-loop interactions in these MDBs which are absent in larger dumbbell structures. Upon slippage of the nascent strand during DNA replication, the formation of MDB has been proposed to be the culprit of repeat expansions. On the one hand, the thermodynamic stability and conformational dynamics of MDB affect the propensity of strand slippage. On the other hand, these structural properties determine whether the MDBs can successfully escape from DNA repair. In this study, we first demonstrate that in addition to regular type II loops, an MDB can also be formed with a quasi-type II loop. Then, we discuss the potential pathways by which the MDBs bring about variable sizes of repeat expansion, high strand slippage propensity and efficient repair escape.

The work described in this abstract was supported by General Research Fund (Project Nos. CUHK14302114 and CUHK14302915) from the Research Grants Council of the Hong Kong Special Administrative Region.

Selected Publications:

- Guo, P. and Lam, S.L. (2016). Unusual structures of CCTG repeats and their participation in repeat expansion. Biomol Concepts doi:10.1515/bmc-2016-0024.
- Guo, P. and Lam, S.L. (2016). Minidumbbell: A New Form of Native DNA Structure. J Am Chem Soc 138, 12534-12540.
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- Chi, L.M. and Lam, S.L. (2005). Structural roles of CTG repeats in slippage expansion during DNA replication. Nucleic Acids Res. 33, 1604-1617.

Biography:

Prof. Sik Lok Lam (Ph.D) was born in Hong Kong in 1970. He received his BSc and PhD from the Department of Chemistry at The Chinese University of Hong Kong in 1992 and 1996, respectively. He proceeded with his postdoctoral research studies first in the Department of Chemistry and Biochemistry at University of Colorado at Boulder in 1996, and then in the Department of Biochemistry and Biophysics at Oregon State University in 1997. He returned to the Department of Chemistry at The Chinese University of Hong Kong as a replacement teacher in 1999, then a tenure-track Assistant Professor in 2003 and became Associate Professor in 2009. He received Wang Tien-Chuan Prize in Spectroscopy from the Committee of Magnetic Resonance in the Chinese Physical Society in 2010. His research focuses on the biophysical chemistry of nucleic acids, especially on sequences which will improve our understanding of the fidelity of DNA replication, molecular mechanism of genetic instabilities, and mechanistic pathways of DNA damage and repair.

TITLE

DNA-encoded libraries (DELs) for lead generation: its impact and recent developments

Abstract :

Novel drug discovery research and activities are characterized with large investment, high risk and long development time, etc as well as facing more challenges. Lead generation is the starting point and one of the most important steps during the early phase of drug discovery R&D, which requires compound library and advanced screening technology and can only be accomplished by some big international pharmaceutical companies with abundance of capital and cutting-edge technology. The emergence of vast DNA Encoded Library has gradually filled the gap in this field and decreased the technological barriers for drug companies at home in the hit identification. As the perfect fusion of Combinatorial Chemicals and High Throughput Sequencing, it not only improves small molecule library to 100Mn even 10Bn, but also makes compound screening more convenient and effective. In this talk, some examples of DEL in drug discovery and technological development will be presented.

Biography:

Dr. Jin Li

Chairman and CEO, HitGen

Dr Li holds 28 years biopharmaceutical experience (at Protherics and AstraZeneca), with senior scientific and leadership roles in early stage research; as well as experience in initiating and leading major collaboration, research and outsourcing programmes. Before founding HitGen, he held Global Director positions of Compound Sciences and Computational Sciences at AstraZeneca. This included responsibility for computational chemistry, computational biology and compound collection enhancement. Dr Li completed his BSc at Sichuan University, and PhD in macromolecular sciences at Aston University. He then completed post-doctoral research in theoretical biochemistry at Manchester University, UK. Dr Li is also a Fellow of the Royal Society of Chemistry, the Guest Professor of Sichuan University and the Expert with Outstanding Contribution to Sichuan Province. He and his team have gained lots of rewards from different levels.

TITLE

Structural basis of DNA capture and gating by gyrase and topoisomerase IV and its inhibition by antibacterial therapeutics.

Ivan Laponogov[1,2], Xiao-Su Pan[2], Dennis Veselkov [2], Isabelle M-T Crevel [1],
Galyna Skamrova [2], Trishant Umrekar [2], Mark R Sanderson [2] and L Mark Fisher [1*],
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[2] Randall Division of Cell and Molecular Biophysics,
Guy's Campus, King's College London, London SE1 1UL, UK.

Abstract:

Gyrase and topoisomerase (topo) IV are bacterial enzymes that mediate DNA supercoiling and chromosome decatenation and are targets for anti-infective therapeutics. The enzymes are structurally related and share a DNA gating mechanism involving a transient covalent enzyme-DNA complex called the 'cleavage complex'. Fluoroquinolone drugs and quinazolinediones stabilise this complex generating a lethal lesion. To understand the reaction cycle and how it is inhibited by drugs, we solved the first crystal structures of drug-DNA cleavage complexes. Here we present structures for gyrase and topo IV allowing comparison of drug binding pockets and details of the cleaved DNA gate. It is believed that topo IV and gyrase act as ATP-operated clamps that function to capture and present DNA for transport via the sequential operation of ATPase, DNA and (ultimately release through the protein) C-gates. We have solved the structure for a three-gate 'open clamp' topo IV-DNA complex at 3.7Å and very recently that of a 'closed clamp' complex. These structures and new biochemical data will be presented and discussed in terms of the insights they provide on the mechanism by which DNA is captured and navigated through these fascinating enzyme machines.

Work has been supported by the Biotechnology and Biological Sciences Research Council, UK.

Selected Publications:

- Laponogov I, Pan XS, Veselkov DA, Cirz RT, Wagman AS, Moser HE, Fisher LM* and Sanderson MR*, Exploring the active site of the Streptococcus pneumoniae topoisomerase IV-DNA cleavage complex with novel 7,8 bridged quinolones ACHN-245 and ACHN-454, Open Biology, 2016, Sep;6(9). pii 160157.
- Veselkov DA, Laponogov I, Pan XS, Selvarajah J, Skamrova GB, Branstrom A, Narasimhan J, Prasad JVNV, Fisher LM* and Sanderson MR*, Structure of a quinolone-stabilized cleavage complex of topoisomerase IV from Klebsiella pneumoniae and comparison with a related Streptococcus pneumoniae complex, Acta Crystallographica Section D, 2016, D72, 488-496.
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- Laponogov I, Pan X-S, Veselkov DA, McAuley K, Fisher LM* and Sanderson MR*, Structural basis of gate-DNA breakage and resealing by type II topoisomerases, PLoS ONE, 2010, 5, e11338, 2010.
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- Pan XS, K Gould and Fisher LM, Probing the differential interactions of quinazolinedione PD 0305970 and quinolones with gyrase and topoisomerase IV, Antimicrob Agents Chemother 2009, 53, 3822-31.
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- Pan XS, Dias M, Palumbo M and Fisher LM, Clerocidin selectively modifies the gyrase-DNA gate to induce irreversible and reversible DNA damage. Nucleic Acids Research 2008, 36, 5516-29.

Biography:

Professor Mark Fisher received his BA degree (in Chemistry) from Oxford University and PhD degree (in Chemistry) from Harvard University (supervisor Prof Jeremy R Knowles, FRS). In 1978, he joined the laboratory of Dr Martin Gellert at NIH, USA to work as a postdoctoral fellow on DNA gyrase supported by a Damon Runyon-Walter Winchell Cancer Fellowship. In 1981, he returned to England to the Biophysics Department of King's College London (Head, Prof Maurice Wilkins, Nobel Laureate) as an independent Cancer Research Campaign Return Fellow. In 1983, he was appointed to a Lectureship in Biochemistry at St George's, University of London, and was promoted to Professor of Molecular Biology in 1996. He was Joint Foundation Director of the Cardiovascular and Cell Sciences Research Institute at St George's and is currently Dean of Research and Deputy Principal. He has served as an Editor for the Biochemical Journal and on the Editorial Boards of AAC and JAC. His main research interests have been the mechanisms of DNA topoisomerases and their role in antibacterial and anticancer drug action and resistance. He has made a number of seminal advances including the double-strand break mechanism of gyrase and topo IV, the characterisation of a human immunoglobulin gene transcriptional enhancer, co-discovery of human topo IIbeta, development of yeast systems for overexpression of human topo IIalpha and beta isoforms and dissection of anticancer drug action, and was first to establish the mutational basis of antibacterial quinolone resistance in many key pathogens that led to the proposal of 'dual targeting' as a strategy to overcome resistance. His current interests focus on understanding the structural basis of the DNA gating mechanisms of gyrase and topo IV and how antibacterials interfere with the reaction. In collaboration with Dr Mark Sanderson of King's College London, he solved the first crystal structures of quinolones and quinazolinediones bound to their topoisomerase-DNA targets- a major breakthrough- as well as the first structure of an 'open clamp' 3-gate topo II-DNA complex, a key reaction intermediate. His work has been supported by BBSRC, Cancer Research UK, and the pharmaceutical industry.

TITLE

Mechanistic insights into metal ion activation and operator recognition by the ferric uptake regulator

Zengqin Deng, Qing Wang, Zhao Liu, Manfeng Zhang, Ana Carolina Dantas Machado,
Wei Wu, Remo Rohs, Ying Li, and **Zhongzhou Chen***,
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Abstract:

Ferric uptake regulator (Fur) plays a key role in the iron homeostasis of prokaryotes, such as bacterial pathogens, but the molecular mechanisms and structural basis of Fur-DNA binding remain incompletely understood. Here, we report high-resolution structures of Magnetospirillum gryphiswaldense MSR-1 Fur in four different states: apo-Fur, holo-Fur, the Fur-feoAB1 operator complex and the Fur-Pseudomonas aeruginosa Fur box complex. Apo-Fur is a transition metal ion-independent dimer whose binding induces profound conformational changes and confers DNA binding ability. Structural characterization, mutagenesis, biochemistry and in vivo data reveal that Fur recognizes DNA by using a combination of base readout through direct contacts in the major groove and shape readout through recognition of the minor groove electrostatic potential by lysine. The resulting conformational plasticity enables Fur binding to diverse substrates. Our results provide insights into metal ion activation and substrate recognition by Fur that suggest pathways to engineer magnetotactic bacteria and antipathogenic drugs.

Work is supported by National Natural Science Foundation of China (31570725, 31370720 and 91519332).

Selected Publications:

◆ Ming-Yan Cheung, Xiaorong Li, Rui Miao, Yu-Hang Fong, Kwan-Pok Li, Yuk-Lin Yung, Mei-Hui Yu, Kam-Bo Wong*, Zhongzhou Chen*, Hon-Ming Lam*. ATP binding by the P-loop NTPase OsYchF1 (an unconventional G protein) contributes to biotic but not abiotic stress responses. PNAS, 2016, 113(10):2648-53.

◆ Lun Jiang, Yibo Chen, Jiangge Zheng, Zhenhang Chen, Yujie Liu, Ye Tao, Wei Wu, Zhongzhou Chen*, Baichen Wang*. Structural basis of reversible phosphorylation by maize pyruvate orthophosphate dikinase regulatory protein. Plant Physiology. 2016, 170(2):732-41.

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Remo Rohs*, Ying Li*, Zhongzhou Chen*. Mechanistic insights into metal ion activation and operator recognition by the ferric uptake regulator. Nature Comm. 2015, Jul 2;6:7642. doi: 10.1038/ncomms8642.

◆ Guoqiang Wang, Qingzhong He, Chong Feng, Yang Liu, Zengqin Deng, Xiaoxuan Qi, Wei Wu, Pinchao Mei, Zhongzhou Chen*. The atomic-resolution structure of human alkb homolog 7 (ALKBH7), a key protein for programmed necrosis and fat metabolism. J Biol Chem. 2014 Oct 3;289(40):27924-36.

◆ Chong Feng, Yang Liu, Guoqiang Wang, Zengqin Deng, Qi Zhang, Wei Wu, Yufeng Tong, Changmei Cheng*, Zhongzhou Chen*. Crystal Structures of the Human RNA Demethylase Alkbh5 Reveal Basis for Substrate Recognition. THE JOURNAL OF BIOLOGICAL CHEMISTRY, 2014 Apr 25;289(17):11571-83

◆ Zengqin Deng, Kathleen C. Lehmann, Xiaorong Li, Chong Feng, Guoqiang Wang,Qi Zhang, Xiaoxuan Qi, Lin Yu, Xingliang Zhang, Wenhai Feng, Wei Wu, Peng Gong, Ye Tao, Clara C. Posthuma, Eric J. Snijder, Alexander E. Gorbalenya, Zhongzhou Chen. Structural basis for the regulatory function of a complex zinc-binding domain in a replicative arterivirus helicase resembling a nonsense-mediated mRNA decay helicase. Nucleic Acids Res. 2014 Mar 1;42(5):3464-77. doi: 10.1093/nar/gkt1310. Epub 2013 Dec 24.

Biography:

Prof. Zhongzhou Chen (Ph.D.) was born in 1974 and raised in Fujian, China. He received his B.S. degree and Ph.D. degree from Tsinghua University in 1997 and 2002, respectively. In 2002, he joined the Department of Immunology at National Jewish Medical and Research Center as a research Associate, in Laboratory of Professor Gongyi Zhang. He was hired in 2007 by College of Biological Sciences, China Agricultural University, as a full professor. He has received several awards, including winners of National Science Fund for Excellent Young Scholars in 2012.

He focused on the structures and function of disease-related proteins, such as the tumor suppressor p53 regulator MDM2 and histone demethylases, and agricultural important proteins. Several structures of proteins and protein complexes were solved and the functions were elucidated. Several enzymatic activity, type of domains and binding modes were uncovered. The specific substrate binding mechanisms were proposed and verified. Several new mechanisms of regulation and recognition were identified. The reasons of mental retardation, cancers and functional loss caused by their mutation were explored. Moreover, Dr. Chen also developed novel methods to improve the quality of protein crystals with the help of the collaborators. Dr. Chen would focus on the regulatory mechanism of important protein complexes, explore the selective recognition of substrates and catalytic mechanism on the structural basis of these important proteins, and uncover the molecular mechanism of regulation, and lay a solid foundation for drug design against diseases, treatment of diseases such as cancers, and agricultural applications.

TITLE

Functional Roles of Local and Global Motions in Nucleic Acids

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Abstract:

Nucleic acids undergo functionally important motions both at the local and global scale. At the local scale, details of base pairing in double-stranded DNA determine protein binding propensity and in RNA they modulate the overall secondary and tertiary structures. At the global scale, supercoils, knots and catenanes are important in a wide range of genetic processes, and global packing is important for the architecture of chromosomes or nucleic acid organization and delivery in viral capsids. The presentation will focus on using molecular dynamics simulations in connection with experimental techniques such as NMR, inelastic neutron scattering and cryo-electron microscopy to address the role of local and global structural dynamics in a number of different nucleic acid systems, including DNA topoisomerase, supercoiled DNA, DNA in viral capsids and non-coding RNAs.

Work is supported by NIH (R01-GM089846) and NSF (CMMI-1404818).

Selected Publications:

◆ H. Zhou, I.J. Kimsey, E.N. Nikolova, B. Sathyamoorthy, G. Grazioli, J. McSally, T. Bai, C.H. Wunderlich, C. Kreutz, I. Andricioaei* and H. M Al-Hashimi*, “m1A and m1G disrupt A-RNA structure through the intrinsic instability of Hoogsteen base pairs,” Nature Structural & Molecular Biology, 23, 803–810 (2016).

◆ E. Ficici, I. Andricioaei and S. Howorka, “Dendrimers in nanoscale confinement: The interplay between conformational change and nanopore entrance,” Nano Letters 15, 4822-4828 (2015). http://dx.doi.org/10.1021/acs.nanolett.5b01960

◆ A.T. Frank, Q. Zhang, H.M. Al-Hashimi, I. Andricioaei, "Slowdown of interhelical motions induces a glass transition in RNA" Biophys. J. 108, 2876-2885 (2015). http://dx.doi.org/10.1016/j.bpj.2015.04.041

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◆ A. Mentes, A.M. Florescu, E. Brunk, J. Wereszczynski, M. Joyeux and I. Andricioaei, “Free energy landscape and characteristic forces for the initiation of DNA unzipping,” Biophys. J. 108, 1727-1738 (2015)

◆ M. Taranova, A. Hirsh, N. Perkins and I. Andricioaei, “Role of microscopic flexibility in tightly curved DNA,” J. Phys. Chem. B, 118, 11028–11036 (2014).

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Biography:

Prof. Ioan Andricioaei (Ph.D.) received his B.S. degree from Alexandru I Cuza University, Iasi, Romania in 1993, his Ph.D. degree from Boston University in 1999, and was a postdoctoral fellow at Harvard University (under the supervision of Professor Martin Karplus, 2013 Nobel Prize winner in Chemistry) until 2003. In 2003, he joined the Department of Chemistry and the Center for Computational Medicine and Biology at the University of Michigan as Assistant Professor, and then moved to the University of California, Irvine in 2007 where he is now Professor of Chemistry and of Physics. He and his research group are interested in computational topics at the interface between molecular biophysics and physical chemistry. Research hinges on a two-fold central theme: (1) developing novel theoretical techniques and (2) applying computer and modeling methods to describe, in terms of dynamics and thermodynamics, biologically important molecular processes, with the aim to explain or predict experimental findings.

Directions include:

1) Computer Simulations of DNA-Binding Machines. Protein-DNA interactions are essential in such crucial cellular functions as replication, repair, transcription or recombination. Many enzymes at and ahead of the replication fork affect large DNA fragments. For instance, topoisomerases undo DNA knotting. Others, like helicases and polymerases, are biomolecular motors: they use the energy of binding and/or hydrolysis of nucleotides to do mechanical work on the DNA fragments to which they bind. Another example is the machinery that compacts DNA inside the capsid of viruses; we have an avid interest in the theoretical description of these fundamental genetic processes through massively parallel computer simulations.

2) Dynamics-Function Relationships in Nucleic Acids. Connections to NMR Relaxation. An accurate measure of free energy, important for biomolecular stability and function, or for ligand binding, has to include the entropy manifested in molecular flexibility. On the experimental side, this dynamic aspect is brought in by developments in solution NMR spectroscopy, which measures motion by relaxation experiments. Molecular dynamics simulation is an important tool to complement these measurements and to connect dynamics to function.

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Chengdu is a City of Culture and History, while Embracing Modernization.

Jin li
锦里

锦里由成都武侯祠博物馆恢复修建，作为武侯祠（三国历史遗迹区、锦里民俗区、西区）的一部分，街道全长550米，现为成都市著名步行商业街，号称『西蜀第一街』，被誉为『成都版清明上河图』。

Kuan zhai xiangzi
宽窄巷子

宽巷子古街市位于成都市蜀都大道西端，
全长约500米。是一处独具老成都民居特色的文明街。

Wu hou ci

武侯祠

成都武侯祠，位于四川省成都市南门武侯祠大街。是纪念中国三国时期蜀汉丞相诸葛亮的祠堂。它是中国唯一一座君臣合祀祠庙和最负盛名的诸葛亮、刘备及蜀汉英雄纪念地，也是全世界影响最大的三国遗迹博物馆。以文、书、刻号称『三绝』的《蜀丞相诸葛武侯祠堂碑》最为知名。

Du fu cao tang

杜甫草堂

杜甫草堂，又称浣花草堂、工部草堂、少陵草堂，位于四川省成都市西郊的浣花溪畔，现今是成都杜甫草堂博物馆，是为了纪念中国唐代伟大现实主义诗人杜甫的博物馆。是当年杜甫流寓成都时的居所，由后人重建得以保存并成为纪念杜甫场所。

The giant panda
breeding research base

大熊猫繁育研究基地

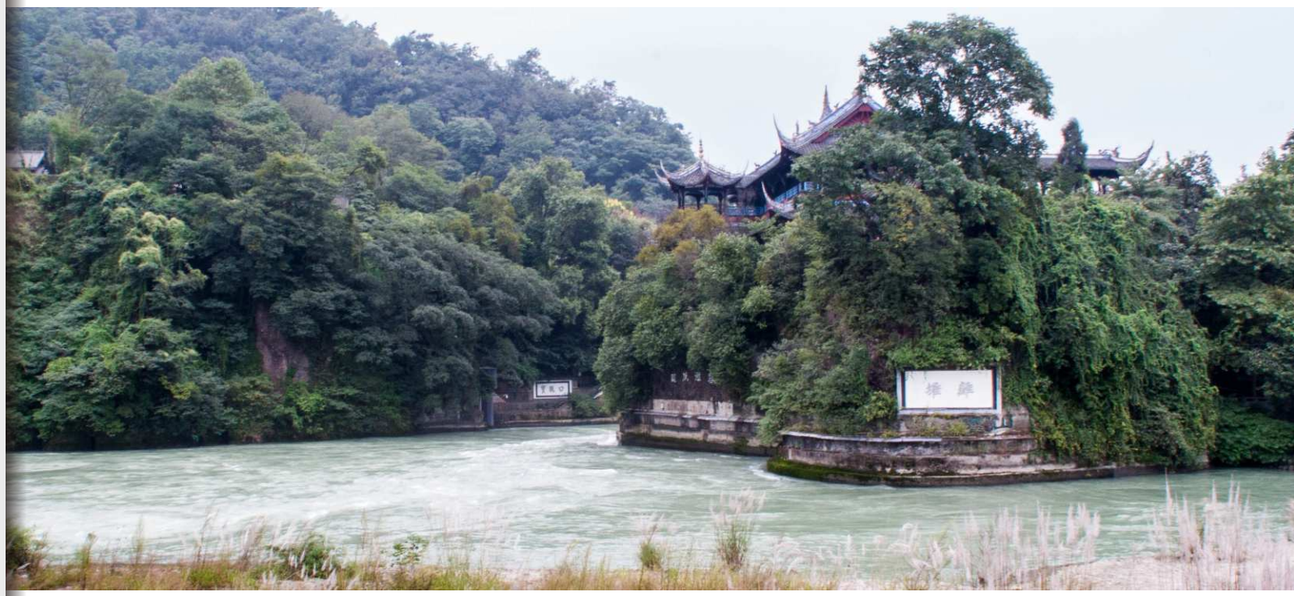
成都大熊猫繁育研究基地，是一个专门从事濒危野生动物研究、繁育、保护教育和教育旅游的非营利性机构。基地位于成都北郊斧头山，距市区10公里。

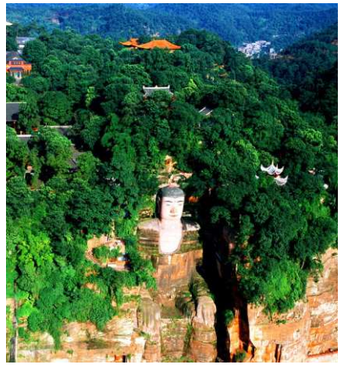
Du jiang yan

都江堰

既是一座岷江上的宏伟水利枢纽，同时也是景色秀丽、文物古迹众多的著名风景名胜区。。

江堰将山水美景充分地融为一体，烟波浩渺，远山如黛，遨游其中充分感受大自然的清新。





Le shan da fo
乐山大佛

乐山大佛，又名凌云大佛，位于四川省乐山市南岷江东岸凌云寺侧，濒大渡河、青衣江和岷江三江汇流处。大佛为弥勒佛坐像，通高71米，是中国最大的一尊摩崖石刻造像。

e mei shan
峨眉山

峨眉山（Mount Emei）位于中国四川省乐山市峨眉山市境内，是中国『四大佛教名山』之一，地势陡峭，风景秀丽，素有『峨眉天下秀』之称，山上的万佛顶最高，海拔3099米，高出峨眉平原2700多米。

FUQIFEIPIAN

夫妻肺片

清朝末年，成都街头巷尾便有许多挑担、提篮叫卖凉拌肺片的小贩。
用成本低廉的牛杂碎边角料，经精加工、卤煮后，切成片，佐以酱油、红油、辣椒、花椒面、芝麻面等拌食，
风味别致，价廉 物美，特别受到拉黄包车、脚夫和穷苦学生们的喜食。20世纪30年代在四川成都有一对摆小
摊的夫妇，男叫郭朝华，女叫张田政，因制作的凉拌肺片精细讲究，颜色金红发亮，麻辣鲜香，风味独特，
加之他夫妇俩配合默契、和谐，一个制作，一个出售，小生意做得红红火火，一时顾客云集，供不应求。

LAOMATUTOU

老妈兔头

老妈兔头是一道四川省特色传统名吃，属于川菜系。
起源于四川省成都市双流县，是当地的招牌美食。
兔头分五香麻辣两种口味，鲜而不腥，色香味形俱佳。

BANGBANGJI

棒棒鸡

棒棒鸡是汉族特色菜肴。属于川菜中的凉菜，主要食材是鸡肉，其味型属于“怪味”，麻、辣、酸、甜、鲜、咸、
香全部味道都具备。棒棒鸡又名“乐山棒棒鸡”、“嘉定棒棒鸡”。
此菜原始于乐山汉阳坝，取用良种汉阳鸡，经煮熟后，用木棒将鸡肉捶松后食用。
在中国烹饪史上，曾有用木棒敲打的名馔“白脯”，见于贾思勰《齐民要术》。
成都棒棒鸡乃四川百年名菜，风味独特、做工精细、选料考究，
是由原汁鸡汤加祖传配方精制而成，与世面上的所谓白斩鸡是有本质区别的。

DANDANMIAN

担担面

担担面汉族特色面食。著名的四川小吃，源起挑夫们在码头挑着担担卖面，所以名为担担面。
用面粉擀制成面条，煮熟，舀上炒制的猪肉末而成。成菜面条细薄，卤汁酥香，咸鲜微辣，香气扑鼻，十分入味。
此菜在四川广为流传，常作为筵席点心。

MAPODOUFU

麻婆豆腐

麻婆豆腐始创于清朝同治元年（1862年），开创于成都外北万福桥边。由于陈麻婆豆腐历代传人的不断努力，
陈麻婆川菜馆虽距今一百四十余年盛名长盛不衰。并扬名海内外，深得国内外美食者好评。
麻婆豆腐也成为了具有四川代表性的名菜，麻婆豆腐是四川省汉族传统名菜之一，属于川菜系。
主要原料为配料和豆腐，材料主要有豆腐、牛肉末（也可以用猪肉）、辣椒和花椒等。
麻来自花椒，辣来自辣椒，这道菜突出了川菜“麻辣”的特点。
此菜大约在清代同治初年（1874年以后），由成都市北郊万福桥一家名为“陈兴盛饭铺”的小饭店老板娘陈刘氏所创。
因为陈刘氏脸上有麻点，人称陈麻婆，她发明的烧豆腐就被称为“陈麻婆豆腐”。