第 106 次生命科学前沿研讨会

The 1st

首届核酸蛋白药物研发国际研讨会

The 1st International Conference on Chemical and Structural Biology of Nucleic Acids and Proteins for Novel Drug Discovery

The 1st International Conference on Chemical and Structural Biology of Nucleic Acids and Proteins for Novel Drug Discovery (June 12-14, 2011, Beijing)

(国际核酸蛋白化学生物学及结构生物学和新药发明研究会议)

六月十二至十四号， 2011 年

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嘉宾简介及论文摘要

Lihe Zhang

Date of Birth : Sept. 8, 1937

Place of Birth: Yangzhou, Jiangsu, China

Current Occupation: Professor, Peking University

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University Education :

1964-1967 Graduate School, Beijing Medical College, got graduate diploma of medicinal chemistry

1954-1958 Department of Pharmacy, Beijing Medical College, China ,

Professional Experience:

2006-date President, Academic Committee of State Key Laboratory of Natural & Biomimetic Drugs,Peking University, Beijing 100083, China

1992-2006 Director, State Key Laboratories of Natural and Biomimetic Drugs, Peking University,Beijing, China

1998-2006 Director, Chemistry Department, National Natural Science Foundation of China

2000- date Professor of Medicinal Chemistry, Peking University

1986-2000 Dean， Professor of Medicinal Chemistry. School of Pharmaceutical Sciences, Beijing Medical University

1983-1986 Associate Professor, School of Pharmaceutical Sciences, Beijing Medical University

1981-1983 Research Associate, Department of Chemistry, University of Virginia, USA

1967-1981 Lecturer, Department of Pharmacy, Beijing Medical College

1958-1964 Assistant, Department of Pharmacy, Beijing Medical College

Scientific Society & Other Committee Activities:

Titular Member, IUPAC, Division III , Biomolecular Chemistry Committee (2006-2008) ; Fellow, Royal Society

of Chemistry (2006-) ; Vice-President, Chinese Pharmaceutical Association(1997-2001) ; President, Asian

Federation for Medicinal Chemistry(1998-2000)

Editorial Boards:

Member, Internat. Adv. Editorial Board, Organic & Biomolecular Chemistry (2006-) , ChemMedChem

(2007-), Medicinal Research Review (2004-), Current Topics of Medicinal Chemistry (2000-)

Research Areas:

Nucleosides and Nucleotides, Anticancer and Antiviral Drugs, Natural Products.

Publications; over 250 in refereed journals.

Awards:

2009 Asia Pharmaceutical Association Nagai-Hisamitsu Outstanding Scientist Award (Osaka, Japan)

2004 Natural Science Award, Second Prize, Ministry of Science and Technology. China

2002 Science and Technology Award, Second Prize, awarded by The Ministry of Education, China

2000 Millennium Pharmaceutical Scientist Award, FIP, San Francisco, USA

1999 He-Liang-He-Li Prize

1998 Science and Technology Award, First Prize, awarded by The Ministry of Education, China

1996 Science and Technology Award, Second Prize, awarded by The Ministry of Education,China-

1995 Member, Chinese Academy of Sciences

1993 12th Edgar Snow Professorship, awarded by Edgar Snow Foundation and University of Missouri,Kansas City , USA

1993 Colorcon Award, International Symposium of International Pharmaceutical Association, Tokyo, Japan

1990 Honorary Doctorate, Hoshi University, Japan

1988 Otani Prize, awarded by Hoshi University, Japan

1980 Beijing Science and Technology Prize, awarded by Beijing City Government, China

1964 National Award for Scientific Research Excellence, State Commission Science & Technology, China

Ada Yonath

Born in Jerusalem, Israel, Prof. Ada Yonath, studied at the Hebrew University, earned Ph.D. degree from Weizmann Institute of Science (WIS) and completed her postdoctoral studies at MIT, USA. She studies protein biosynthesis, focusing on ribosomes, which translates the genetic code into proteins, and on their inhibition by antibiotics, including mechanisms for acquiring resistance.

She is using X-ray crystallography supported by molecular biology, mutagenesis and other biophysical methods. For this aim, she established in the seventies the first laboratory for protein crystallography in Israel, which was the only laboratory of this kind in the country for almost a decade.

She is a professor of structural biology at WIS, holds the Kimmel Professorial Chair, and directing the Kimmelman Center for Biomolecular Structure and Assembly. In 1986-2004 she also headed the Max-Planck Research Unit in Hamburg, Germany.

She is a member of the US National Academy of Sciences (NAS); the American Academy of Arts and Sciences; the Israel Academy of Sciences and Humanities; the European Academy of Sciences and Art; the European Molecular Biology Organization; and the International Academy of Astronautics. Additionally, she has honorary doctorates from Tel Aviv, Ben Gurion, Bar Ilan and Oxford Universities.

Her awards include the 1st European Crystallography Prize; the Israel Prize; The Paul Karrer Gold Medal, Zurich, Switzerland; the Louisa Gross Horwitz Prize, NYC; the Paul Ehrlich-Ludwig Medal, Germany; the Wolf Prize; the UNESCO Award for Women in Science Prize; the Albert Einstein World Award of Science; the Erice Prize for Peace and the Nobel Prize for Chemistry.

From basic science to improved ribosomal antibiotics

Ada Yonath

Department of Structural Biology, Weizmann Institute, Rehovot 76100, Israel

Ribosomes are the universal cellular machines that translate the genetic code into proteins. They posses spectacular architecture accompanied by inherent mobility that facilitate their smooth performance in decoding, peptide bond formation and nascent protein elongation. Owing to their fundamental role, ribosomes are targeted by many antibiotics, which paralyze the ribosomes by binding to their functional sites. The structural bases for the antibiotics binding modes, inhibitory action and synergism pathways were revealed by analyzing crystal structures of complexes of antibiotics with ribosomal particles. Issues concerning strategies for differentiation between ribosomes of patients and pathogens, and mechanism leading to bacterial resistance to antibiotics will be discussed.

Yigong Shi (施一公)

Dr. Yigong Shi is a University Professor and Dean of the School of Life Sciences at Tsinghua University. He received his Bachelor's Degree with highest honor from Tsinghua University in 1989 and Ph.D. in Biophysics at Johns Hopkins University School of Medicine in 1995. He performed his post-doctoral research at the Memorial Sloan-Kettering Cancer Center. He joined Princeton University as an Assistant Professor in 1998 and was promoted to Full Professor in 2003. He was named the Warner-Lambert/Parke-Davis Professor of Molecular Biology at Princeton University in 2007. Dr. Shi declined an offer as an investigator of the Howard Hughes Medical Institute and returned to Tsinghua University in 2008.

Dr. Yigong Shi's research has provided important insights into programmed cell death, protein phosphatase 2A, and regulated intramembrane proteolysis. His pioneering research on caspase activation, inhibition, and derepression markedly advanced mechanistic understanding of programmed cell death. He is a leader in the structural biology of cell signaling and macromolecular assemblies. He was a Searle Scholar and a Rita Allen Scholar. He authored more than 120 research papers, including 34 in *Cell*, *Nature*, and *Science*. For his research contributions, Dr. Shi received a number of recognitions, including the 2003 Irving Sigal Young Investigator Award from the Protein Society and the 2010 Sackler Prize in Biophysics. Yigong Shi is an elected fellow of the American Association for the Advancement of Science (AAAS).

Mechanisms of Programmed Cell Death through Structural Biology

Yigong Shi

School of Life Sciences, Tsinghua University, Beijing 100084, China

Programmed cell death, also known as apoptosis, is central to the development and homeostasis of metazoans. Dysregulation of apoptosis leads to a variety of human pathologies, including cancer, autoimmune diseases, and neurodegenerative disorders. Since the concept of apoptosis was established in 1972, research efforts have led to the identification of hundreds of genes that govern the initiation, execution, and regulation of apoptosis primarily in three model organisms: Caenorhabditis elegans, Drosophila melanogaster, and mammals. The central pathway of apoptosis is conserved among the three organisms and involves the activation of cell-killing proteases known as caspases. In this lecture, I describe systematic characterization of the molecular mechanisms of programmed cell death by an integrated approach of structural biochemistry and biophysics.

Adrian R. Ferré-D'Amaré

Adrian R. Ferré-D'Amaré, Ph.D., is Senior Investigator and Chief of the Laboratory of RNA Biophysics and Cellular Physiology at the National Heart, Lung and Blood Institute (NHLBI). He was born in Tokyo, and is a dual citizen of México and the USA. After carrying out research in marine ecology as a teenager and in college, he graduated with a B.S. in chemistry from the Instituto Tecnológico de Monterrey. He received his Ph.D. in molecular biophysics from The Rockefeller University. Following a post-doctoral stay at Yale University, he joined the Fred Hutchinson Cancer Research Center as an Assistant Member in 1999. He was promoted to Associate Member in 2003 and to Full Member in 2008. He was a Distinguished Young Scholar in Medical Research of the W.M. Keck Foundation in 2003-2008, received the Eli Lilly & Co. Research Award from the American Society for Microbiology in 2004, and was appointed Investigator of the Howard Hughes Medical Institute (HHMI) in 2008. He resigned from HHMI in 2011 to pursue opportunities in molecular biophysics and riboregulation at NHLBI.

Crystallographic and fitness landscape studies of catalytic and gene-regulatory RNAs

Adrian R. Ferré-D'Amaré

Laboratory of RNA Biophysics and Cellular Physiology National Heart, Lung and Blood Institute 50 South Drive, MSC-8012 Bethesda, MD 20892-8012, USA

Like proteins, RNA has the remarkable ability to fold into complex structures capable of orienting functional groups precisely and binding to other molecules with high specificity and affinity. This is most starkly demonstrated by ribozymes (catalytic RNAs) and riboswitches (small molecule-responsive gene-regulatory mRNA domains) that can carry out their biochemical functions in the absence of any auxiliary proteins. This talk will review crystallographic and biochemical studies of the *glmS* ribozyme-riboswitch, a catalytic RNA that regulates expression of a key enzyme in the synthesis of the cell wall in gram-positive bacteria. Crsytallographic and biochemical studies reveal that this RNA employs a small molecule, glucosamine-6-phosphate (GlcN6P), as a catalytic cofactor. However, the ribozyme is not a passive scaffold, as the chemical properties of GlcN6P are modulated by binding to the RNA. We will also review recent studies that combine *in vitro* selection and next-generation DNA sequencing to characterize the fitness landscape of ribozymes. The fitness landscape describes the relationship between all possible genotypes of a macromolecule and the corresponding phenotypic fitness. Our methodology makes it possible to describe the fitness landscape of an RNA (determining the activity of several million possible genotypes) in a single experiment. This amounts to performing quantitative biochemistry through sequencing. We find that the fitness landscape of an RNA ligase ribozyme is very rugged; that is, small changes in the genotype result in large changes in activity. The structural underpinnings of this finding will be discussed.

Runsheng Chen (陈润生)

Professor Runsheng Chen is now Professor in Systems Biology Research Center and State Key Laboratory of Biomacromolecules at the Institute of Biophysics, Chinese Academy of Sciences. He is also a member of Human Genome Organization (HUGO), and a member of the biomacromolecule group of The Committee on Data for Science and Technology (CODATA). From 1992 to 1996 he was member of the biophysics professional committee of the International Union of Pure and Applied Physics (IUPAP), and is now the General-secretary and Vice president of Chinese Society of Biophysics. He graduated in 1964 from the Department of Biophysics of the University of Science and Technology of China. From 1985 to 1987 he studied the electronic structure of biomacromolecules at the University Erlangen-Nurnberg, as a fellow of the Alexander von Humboldt foundation. After that he has been engaged in research cooperation with the Hong Kong University of science and technology, The Chinese University of Hong Kong, Osaka University in Japan, Erlangen-Nurnberg University, University of California, Los Angeles, and Harvard University. In October 1996, Prof. Chen was invited to give a lecture called“From DNA sequence database to protein three-dimensional structure” at the 15th international CODATA conference, and won the “Kotani Prize”. In 2007, he was elected as Member of the Chinese Academy of Sciences. Professor Chen was awarded” Ho Leung Ho Lee Prize” in 2008.

Prof. Chen has occupied with studies in bioinformatics over a number of years. He was the first in China to accomplish the assembly and gene annotation of a complete bacterial genome. He has further established statistical DNA sequence analysis, fractal dimension analysis, and work on neural networks, complexity, local area degeneracy factor analysis, cryptology and other methodologies. Among these, prof. Chen was the first time set up cryptology studies in China. He also took part in the sequencing of 1% of the human genome and computer analysis of the rice genome draft. For 20 years, Prof. Chen has taken a systematic study in the field of bioinformatics, and published more than 120 SCI papers; besides, he was invited to give report at international academic conference many times.

The intermediate-size noncoding RNA

Runsheng CHEN

(Institute of Biophysics, Chinese Academy of Sciences, Beijing 100101)

Recent years have witnessed an expanding universe of small non-coding RNAs (ncRNAs), but apart from a few well-studied classes, for most of these RNAs our present knowledge with respect to biogenesis, regulation, structure and function is still limited. To study further these aspects of small ncRNAs, we have cloned 100 novel and 61 known or predicted *Caenorhabditis elegans* full length ncRNAs, and studied their genomic environment and transcriptional characteristics. We find that 2/3 of all the ncRNAs, including many intronic snoRNAs, are independently transcribed under the control of ncRNA specific upstream promoter elements, and at least 60% of the ncRNAs appears to be developmentally regulated. Most of the novel ncRNAs are conserved in *C. briggsae*, but only one homologue was found outside the nematodes. Estimates indicate that the *C. elegans* transcriptome contains approximately 2500 small non-coding RNAs, with a considerable potential for acting as regulatory elements in nematode development.

The 1st international conference on chemical and structure biology of nucleic acids and protein for novel drug discovery June 12-14, 2011, Beijing

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Principal Investigator, Institute for Integrated Cell-Material Sciences (iCeMS).

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EDUCATIONAL BACKGROUND:

1979	B.S. Kyoto Univ. Department of Synthetic Chemistry.
1981	M.S. Kyoto Univ. Department of Synthetic Chemistry.
1984	Ph. D. Kyoto Univ. (Prof. T. Matsuura: Organic Chemical Approaches to DNA Photochemistry-New Aspects of Thymine Photochemistry)

PROFESSIONAL BACKGROUND:

1984	Research Associate at University of Virginia (USA) (Prof. S. M. Hecht: Mechanism of Action of Antitumor Antibiotics Bleomycins)
1986	Research Associate at Kyoto University (Prof. T. Matsuura)
1987	Assistant Professor, Kyoto Univ. Department of Synthetic Chemistry (Prof. I. Saito)
1993	Associate Professor, Kyoto Univ. Department of Synthetic Chem. & Biological Chem.
1996	Professor, Tokyo Medical & Dental Univ. Institute of Biomaterials & Bioengineering.
2003	Professor, Kyoto Univ. Graduate School of Science, Department of Chemistry.
2008	Principal Investigator, Institute for Integrated Cell-Material Sciences (iCeMS).

AWARDS:

1999	Nippon IBM award
2005	The Creative Work Award of Chemical Society of Japan

SERVICE:

Editorial Advisory Board of ChemBioChem (2005~).
Editorial Advisory Board of J. Am. Chem. Soc. (2009~).
Editorial Board of J. Nucleic Acids (2009~).
Editorial Board of The Chemical Record (2011~).
Editorial Advisory Board of J. Med. Chem. (2011~).
Publications author or co-author of ~190 original papers including 53 J. Am. Chem. Soc.

Chemical Biology that Controls DNA Structure and Function

Hiroshi Sugiyama[1,2]

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Fifty years after the discovery of the double-helical structure of DNA, the complete sequence of the human genome has been determined. Many diseases, including cancer, hereditary, and viral diseases, can now be understood at the DNA sequence level. Recently, it has been revealed that epigenetic modification plays an important role in gene expression, which controls the gene expression through DNA methylation and histone modification. This is closely related to the cell reprogramming and differentiation. We have been undertaking original research on the molecular recognition of DNA by antitumor antibiotics, and the analysis of atom-specific chemical reaction toward DNA with these agents.[1] By reconstituting such knowledge, various functionalized sequence-specific DNA binders were synthesized as an artificial genetic switch.[2] Also, we have been studying hydrogen abstraction by the uracil radical generated by photoirradiation of 5-halouracil-containing DNA, and found that hydrogen abstractions strictly reflect DNA conformation.[3] Thus, we proposed a photochemical method for the analysis of local conformation of DNA. Furthermore we have demonstrated to control the reactions with DNA methylase and repair enzymes in a designed DNA nanostructure, DNA origami, and analyzed the single reaction using high-speed atomic force microscope (AFM).[4] Recent progress of regulation of the epigenetic gene expression using designed molecules, and elucidation the mechanism using single molecular imaging technique will be discussed.

1. Sugiyama, H. ***Bull. Chem. Soc. Japan*** **2007**, 80, 823-841.
2. Bando, T.; Sugiyama, H. ***Acc. Chem. Res.*** **2006**, *39,* 935-944.
3. Xu, Y.; Tashiro, R.; Sugiyama, H. ***Nature Protocols*** **2007**, 2, 78-87.
4. (a) Endo, M.; Katsuda, Y.; Hidaka, K.; Sugiyama, H. ***J. Am. Chem. Soc.*** **2010,** *132,* 1592-1597. (b) Sannohe, Y,; Endo, M,; Katsuda, Y,; Hidaka, K,; Sugiyama, H. ***J. Am. Chem. Soc*** **.2010,** *132*,16311-16313. (c)Wickham, S.; Endo, M.; Katsuda, Y,; Hidaka, K.; Bath, J.; Sugiyama, H.; Turberfield, A.J. ***Nature Nanotech,*** **i**n press.

Steven A. Benner

Dr. Steven A. Benner is a Distinguished Fellow at the Foundation for Applied Molecular Evolution and The Westheimer Institute of Science & Technology, which he cofounded. His research spans many fields in the physical sciences and natural history. His early work in synthetic biology generated, in 1984, the first synthetic gene encoding an enzyme, strategies for the total synthesis of genes that are today widely used, a redesigned DNA that incorporates twelve nucleotides, expanded genetic systems that encode proteins with more than 20 amino acids, nanostructures that exploit these, and some of the first designed enzymes. From these, his laboratory has constructed artificial chemical systems capable of supporting Darwinian evolution and tools that today help personalize the care of some 400,000 patients annually. His laboratory also helped found the field of paleogenetics, which resurrects ancestral genes and proteins from extinct organisms for study in the laboratory, providing strategies to test historical hypotheses throughout basic and biomedical research and in fields such as mammalian reproduction, hypertension, and alcoholism. In collaboration with Gaston Gonnet, the Benner laboratory developed evolutionary bioinformatics, completing in 1990 the first exhaustive matching of a modern genomic sequence database, developing advanced models for patterns of sequence divergence in genes and proteins, coupling bioinformatics models for protein divergence with protein function, and providing the first successful tools to predict protein folds from sequence data alone. This work also marketed the first evolutionary organized genomic database, the MasterCatalog.

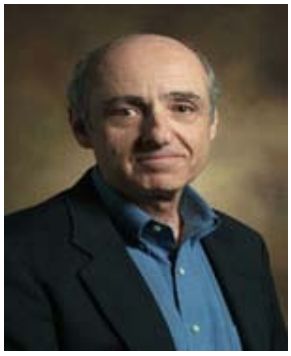
Modern synthetic biology. Darwin from the atom up

Steven A. Benner

Foundation for Applied Molecular Evolution (www.ffame.org), Gainesville FL 32601

The term "synthetic biology" was coined by Waclaw Szybalski in 1974 to describe recombinant DNA technology used to rearrange natural genes and proteins in new cellular contexts. The apotheosis of this classical synthetic biology is current work of Venter, Smith, and their colleagues, who are rearranging genes from natural biology on the scale of a whole microbial genome. Chemists use the term differently, however, with the goal being to create new chemical compounds without relying on genes delivered by billions of years of biological evolution to reproduce behaviors from biology of increasing complexity, from the design of enzymes and genetic systems to constructing artificial chemical systems capable of Darwinian evolution. The last, when presented as a "grand challenge", forces scientists across uncharted terrain where they must solve unscripted problems in ways that test underlying theory. If the theory is inadequate, the synthesis fails, and fails in a way that cannot be overlooked (as is the human propensity). Thus, synthesis can drive discovery and paradigm change in ways that analysis cannot. This talk will describe recent efforts to meet this grand challenge in synthetic biology. We have asked: Can we build a molecular system that directs its own inheritance with heritable mutations, and displays phenotypes that can be selected? We will describe synthetic systems that do so, in the laboratory, and what it says about life as a universal.

Sidney M. Hecht



Sidney Hecht obtained his Ph.D. in Chemistry at the University of Illinois. Following studies as an NIH Postdoctoral Fellow in Molecular Biology at the University of Wisconsin, he accepted a position on the MIT Chemistry faculty in 1971. In 1979 he moved to the University of Virginia, where he was the John W. Mallet Professor of Chemistry and Professor of Biology until 2008. From 1981-87 he held concurrent appointments at Smith Kline & French Laboratories, first as Vice President Preclinical R&D, then as Vice President Chemical R&D. Since 2008 he has been Director of the Center for BioEnergetics in the Biodesign Institute, and Professor of Chemistry at Arizona State University. He has been an Alfred P. Sloan Fellow, and a John Simon Guggenheim Fellow. During 1991 he was a Professor Associé at the Muséum National d'Histoire Naturelle in Paris and Gastprofessor at the Eidgenössische Technische Hochschule in Zürich. He has held more than 25 lectureships at other universities. He received the 1996 Cope Scholar Award of the American Chemical Society and was selected as Virginia's Outstanding Scientist for 1996. More recently he received the 1998 Research Achievement Award of the American Society of Pharmacognosy. He was elected a Fellow of the American Association for the Advancement of Science in 2004, and a Fellow of the American Society of Pharmacognosy in 2007.

He has served as a member of numerous Scientific Advisory Boards, and has helped to found three companies. He has been an Associate Editor of the *Journal of the American Chemical Society* since 1992 and has served on the Editorial Advisory Boards of *Bioconjugate Chemistry, Chemical Research in Toxicology, Medicinal Chemistry Research, Journal of Molecular Recognition, Molecules Online, Molecular Cancer Therapeutics, Oncology Research/Anticancer Drug Design* and *Current Medicinal Chemistry-Anticancer Agents.*

His research interests include the synthesis and mechanism of action of bleomycin group antibiotics; accomplishments include a total synthesis of bleomycin, and a detailed description of the way in which bleomycin is activated, binds to DNA and RNA and destroys these macromolecules. He has also identified DNA topoisomerase I as the cellular locus for the action of the alkaloid camptothecin and participated in the discovery and development of the camptothecin analogue topotecan, which is now marketed under the tradename Hycamtin for the treatment of ovarian cancer and small cell lung cancer. At the Biodesign Institute, his Center is studying the chemistry of the mitochondrial electron transport chain with the goals of understanding the factors that limit mitochondrial efficiency, and devising therapeutic strategies to treat mitochondrial dysfunction. Research interests pertinent to this conference have included the use of misacylated transfer RNA's in cell free protein biosynthesizing systems for the elaboration *in vitro* of peptides and proteins containing synthetic amino acids at defined positions. As part of this effort, he has devised a method for reengineering the bacterial ribosome to enable the incorporation of non alpha-amino acids into proteins.

Reengineering the Bacterial Ribosome

Larisa Dedkova, Liqiang Zhang, Nour Eddine Fahmi, Melissa del Rosario and Sidney M. Hecht

Center for BioEnergetics, Biodesign Institute, Arizona State University,

Tempe, AZ, USA

In a previous effort, we have described modifications in 23S ribosomal RNA that enabled us to prepare modified ribosomes capable of the enhanced incorporation of D-amino acids into proteins. Incorporation of D-phenylalanine and D-methionine into predetermined positions of dihydrofolate reductase and firefly luciferase afforded modified enzymes whose functions were studied. Some positions in the proteins proved to be surprisingly tolerant of a change in chirality of the incorporated amino acid, while others resulted in a significant diminution of function. The procedure employed for identification of the modified ribosomes involved a survey of bacterial colonies harboring plasmids with the gene for the modified 23S rRNAs for altered growth rates and sensitivity to chloramphenicol.

Presently, we describe modification of the 23S rRNA at multiple sites to facilitate enhanced incorporation of beta-amino acids into proteins. The procedure employed utilizes iterative DNA mutations, introduction of the plasmids containing the modified 23S rRNA gene into bacteria, and a mechanistically focused selection of colonies exhibiting enhanced recognition of beta-amino acids. Also developed has been a new assay that enables direct verification of the ability of the modified ribosomes to incorporate beta-amino acids. The modified ribosomes incorporate the beta-amino acids with significantly enhanced efficiency relative to wild-type ribosomes without undue non-specific codon readthrough, and retain their ability to produce unmodified proteins of good quality.

*L. M. Dedkova, N. E. Fahmi, S. Y. Golovine and S. M. Hecht, Efficient D-Amino Acid Incorporation into Protein by Modified Ribosomes, J. Am. Chem. Soc., **125**, 6616-6617 (2003).*

*L. M. Dedkova, N. E. Fahmi, S. Y. Golovine and S. M. Hecht, Construction of Modified Ribosomes for Incorporation of D-Amino Acids into Proteins, Biochemistry, **45**, 15541-15551 (2006).*

Zicai Liang (梁子才)

Prof. Liang received his PhD from Uppsala University in Sweden in 1995. After his PhD, he underwent postdoctoral training for three years in Yale University before taking on faculty positions. He is currently Professor of Biotechnology at Institute of Molecular Medicine, Peking University. Dr Liang's research interests include application of siRNA and other nucleic acid tools in biomedical research and translational applications, especially in vivo application of siRNA for drug target validation and siRNA drug development.

Site specific degradation of dsRNA by RNase A and rational modification for stablizing siRNA in drug development

Zicai Liang

Double-stranded small interfering RNAs (siRNAs) are important modulators of biological processes and hold great promise for therapeutic applications. However, serum processing of synthetic siRNAs is still largely unknown. To address this issue, serum degradation assays of 125 siRNAs were first performed in this study. Four siRNA categories of distinct serum stability were identified, including a group of siRNAs that were stable in their native form for both in vitro and in vivo assays. Fine mapping of the cleavage events occurring in serum treatment demonstrated that most occurred at two vulnerable sites, leading to a speculation that rational modification of these sites might protect most siRNAs from serum degradation. For proof of concept, an exhaustive siRNA modification study was performed. In addition to the consistent stabilization pattern revealed at these sites, our study further showed that a single modification made at the cleavage site stabilized the siRNAs to a large extent, highlighting the importance of these sites in siRNA degradation. In summary, the present study provided a comprehensive picture of serum processing of siRNA as well as a starting point for a rational siRNA modification strategy, both of which are of great importance to in vivo and therapeutic applications of siRNA.

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1988	MS	Nankai University
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1983-1985		Teacher, Hubei Medical School
1988-1990		Engineer, Beijing Chemical Reagent Company
1994-1997		Research Fellow, Harvard Medical School
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2001-		Professor, IEOC, College of Chemistry, NKU

Research Interests:

1. Chemical Biology of Bioactive Molecules:
2. Chemical Biology of Nucleic Acid
3. Molecular basis of pesticide action and pesticide resistance

Selected Publications:

1. Xiaohong Qin, Ying Tan, Lele Wang, Zhifang Wang, Baifan Wang, Xin Wen, Guangfu Yang, Zhen Xi*, and Yuequan Shen*, Structural Insight into Human Variegate Porphyria Disease, FASEB J. **2011**, 25(2), 653-664, Epub on November 3, 2010 as doi: 10.1096/fj.10-170811.
2. Junmei Hong, Jun Li, Fan Yi, Huang Huang, Na Wei, Yuanyu Huang, Jie Zheng, Yongqiang Shan, Mingrui An, Yong-Yan Zhang, Jianguo Ji, Peizhou Zhang, Zhen Xi, Quan Du*, Zicai Liang*, Comprehensive analysis of sequence-specific stability of siRNA, FASEB J. **2010**, 24(12), 4844-4855, Epub on August 23, 2010 as doi:10.1096/fj.09-142398.
3. Bing Wang, Liqiang Cao, William Chiuman, Yingfu Li*, Zhen Xi* Probing the Function of Nucleotides in the Catalytic Cores of the 8-17 and 10-23 DNAzymes by Abasic Nucleotide and C3 Spacer Substitutions. *Biochemistry*, **2010**, 49 (35), 7553–7562, DOI: 10.1021/bi100304b.
4. Xiaohong Qin, Lu Sun, Xin Wen, Xue Yang, Ying Tan, Hao Jin, Qiongyao Cao, Weihong Zhou, Zhen Xi*, Yuequan Shen*. Structural insight into unique properties of protoporphyrinogen oxidase from Bacillus subtilis. *Journal of Structural Biology*, **2010**, *170*, 76-82.
5. Long Yi, Heyang Li, Lu Sun, Liangliang Liu, Caihong Zhang, and Zhen Xi*. A Highly Sensitive Fluorescence Probe and Its Applications for Fast Thiol-Quantification Assay of Glutathione Reductase *Angew. Chem.* **2009**, *48* (22), 4034 – 4037.
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Ribosome Translocation and Antibiotics

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Ribosome, the machine of protein biosynthesis, is one of the major proven drug targets by antibiotics. Antibiotics targeting on ribosome are less prone to develop cross resistance. Ribosome is a very good target to develop antibiotics. Sparsomycin, a broad-spectrum antibiotic,[1,2] binding at the peptidyl transferase centre (PTC) of the large subunit of ribosome,[3-5] inhibits protein synthesis through hindering peptide bond formation.[6,7] Recently, Fredrick and Noller reported an interesting biological function of sparsomycin, namely catalyses translocation in the absence of elongation factor G (EF-G) and GTP.[8] Translocation, which is normally catalyzed by EF-G, with GTP hydrolyzed to GDP, is the coupled movement of mRNA:(tRNA)2 complex by one codon on ribosome after the formation of each peptide bond. The fact that translocation can be catalyzed by sparsomycin implies that translocation is the inherent function of ribosome, and suggests the involvement of PTC in the process of translocation.[8] In view of the importance of ribosome in antibiotic drug development, a clearer mechanistic understanding of ribosome translocation process might be providing a potential target site to design new antibiotic drugs.

Based on the crystal structure of ribosome with sparsomycin, it has been proposed that sparsomycin promoted the ribosome translocation by decreasing the activation energy for translocation and trapping ribosomes in the post-translocation state.[8,9] However, how the interactions between such a small molecule and the ribosome complex induce the movement of tRNA and mRNA is still unclear. In order to gain the understanding for this phenomenon, we studied how the structure, especially the chiral centers, of sparsomycin affects the ribosomal translocation activity. Our results demonstrated that the effects of sparsomycin analogues on conversion between pre- and post- translocation ribosome showed their preference interaction for the post state. The chirality, especially of the Sc, is important for sparsomycin to stabilize ribosome in the post state, and therefore promote the forward and inhibit the reverse translocation. The sparsomycin analogues showing stronger promotion to forward translocation make stronger inhibition to reverse translocation, which is in accordance with stronger binding ability to ribosome, and stronger antibacterial activities.

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8. Fredrick, K.; Noller, H.F. *Science* **2003**, *300*, 1159.
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EDUCATION

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1982-1985 M.S. in Biophysics Department of Virology, Wuha University, P. R. China.

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EXPERIENCE

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1993-1996 Visiting Fellow Laboratory of Cellular and Molecular Pharmacology, National Institute of Environmental Health Sciences, Research riangle Park, North Carolina 27709, U. S. A.

1991-1993 Research Associate Department of Botany, North Carolina State University, Raleigh, NC 27695-7612, U.S.A.

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PAPERS:

1. Xue, Y., Liu, J.-q., Zheng, K.-w., Kan, Z.-y., Hao, Y.-h., & Tan, Z., (2011) Kinetic and Thermodynamic Control of G-Quadruplex Folding. *Angew. Chem. Int. Ed.*, (In press).
2. Zheng, K.W., Zhang, D., Zhang, L.X., Hao, Y.H., Zhou, X.A., & Tan, Z., (2011) Dissecting the Strand Folding Orientation and Formation of G-Quadruplexes in Single- and Double-Stranded Nucleic Acids by Ligand-Induced Photocleavage Footprinting. *J. Am. Chem. Soc.*, 133(5): 1475-83.
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11. Yao, Y., Wang, Q., Hao, Y.H., & Tan, Z., (2007) An exonuclease I hydrolysis assay for evaluating G-quadruplex stabilization by small molecules. *Nucleic Acids Res.*, 35(9): e68.
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15. Zhao, Y., Kan, Z.Y., Zeng, Z.X., Hao, Y.H., Chen, H., & Tan, Z., (2004) Determining the folding and unfolding rate constants of nucleic acids by biosensor. Application to telomere G-quadruplex. *J. Am. Chem. Soc.*, 126(41): 13255-64.
16. Yuan, B.F., Hao, Y.H., & Tan, Z., (2004) Universal sensing strategy for the detection of nucleic acid targets by optical biosensor based on surface plasmon resonance. *Clin. Chem.*, 50(6): 1057-60.

Targeting telomere G-quadruplex as an anti-cancer strategy

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Because of the end-replication problem, telomere DNA in animal cells shortens in each round of DNA replication at cell division. In > 85% cancer cells, telomere length homeostasis is maintained by telomerase, a ribonucleoprotein that synthesizes telomere repeats onto telomere ends. Human telomere DNA carries a 3' single-stranded G-rich DNA tail of ~200 nucleotides. In the rest of cancer cells, telomere extension is carried out by the alternative lengthening of telomeres (ALT) mechanism in which the 3' tail invades the duplex region of telomeric DNA and hybridizes to the C-rich strand to perform templated extension. Telomere extension by telomerase or the ALT mechanism requires a minimal 3' tail of 8 or 12 nucleotides. In the presence of K+, which is abundant in animal cells, the G-rich strand of telomere DNA can fold into a four-stranded structure called G-quadruplex. Telomere G-quadruplex preferentially forms at the farthest 3' end and minimizes the 3' tail. As a result, G-quadruplex formation in telomere DNA effectively inhibits telomere extension by both telomerase and the ALT mechanism. For this reason, telomere G-quadruplex stabilization by small chemical ligands is being enthusiastically explored as a novel chemotherapeutic strategy against cancer. A growing number of ligands have been identified to stabilize G-quadruplex, inhibit telomerase-mediated telomere extension and induce growth arrest, senescence or apoptosis in cancer cells. In comparison with catalytic inhibitors to telomerase, which may suffer from potential risk of selecting for or inducing the ALT mechanism, telomere G-quadruplex stabilizers is anticipated to inhibit telomere extension by both telomerase and the ALT, thus potentially providing a more secure strategy for disrupting telomere homeostasis. However, recent examination of the specificity of G-quadruplex ligands shows that such ligands are much more than G-quadruplex stabilizers with strong off-target effect. They are found to inhibit telomerase-mediated telomere extension via multiple pathways among which stabilization of telomere G-quadruplex may only make a minor or neglectable contribution.

David M. J. Lilley

EDUCATION

1966-1969 B.Sc in Chemistry, University of Durham. 1st Class honours.

1969-1972 Ph.D. in Physical/Theoretical Chemistry, University of Durham.

1972-1973 M.Sc. in Biochemistry, University of London, Distinction.

APPOINTMENTS

1981-1984 Lecturer in Biochemistry, University of Dundee.

1984-1989 Reader in Biochemistry, University of Dundee.

1989-present Professor of Molecular Biology, University of Dundee.

1993-present Director, CR-UK Nucleic Acid Structure Research Group.

HONOURS ETC.

1989 Awarded Personal Chair in Molecular Biology

1994 Awarded Gold Medal of Gregor Mendel by Czech Academy of Sciences

1996 Awarded Gold Medal of V. Prelog in Stereochemistry by the ETH, Zürich.

2001 Award in RNA and Ribozymes by the Royal Society of Chemistry, London

2002 Elected a Fellow of the Royal Society

2003 Fellow of the Royal Society of Chemistry.

2006 Royal Society of Chemistry Interdisciplinary Award.

MAJOR RESEARCH ACHIEVEMENTS

1. Description of four-way helical junctions in molecular terms. A structural basis for thinking about genetic recombination.
2. Description of the interaction between DNA junctions and resolving enzymes. Crystal structure of the junction-resolving enzyme T7 endonuclease I.
3. First experimental demonstration of the existence of cruciform structures, and elucidation of their extrusion pathways.
4. Demonstration of topological coupling between prokaryotic promoters; the leu-500 promoter
5. Elucidation of the NMR and crystal structure of the parallel-stranded guanine tetraplex
6. Structure of bulged RNA molecules; first solution measurement of the helical repeat of RNA.
7. The solution structure of the hammerhead and hairpin ribozymes, and the relationship between RNA structure and catalysis. Single molecule enzymology and mechanism of the hairpin ribozyme.
8. Structure folding, active site and mechanism of the VS ribozyme
9. Structure and folding of K-turn RNA, and induced fit by proteins.
10. The use of fluorescence resonance energy transfer as a powerful structural method in nucleic acids.

320 scientific papers published and 15 books edited

Frequent invited presentations at meetings on nucleic acid structure, RNA catalysis and recombination.

The structure, folding and protein binding of k-turns in RNA

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The kink-turn (k-turn) is a widespread and important element in the architecture of RNA molecules. First discovered in multiple examples in the ribosome, the k-turn generates a local kink in an RNA helix of 60° (included angle). In addition to the ribosome, k-turns occur in box C/D and H/ACA snoRNA, the U4 snRNA and some riboswitches. They are therefore important in translation, RNA modification and splicing, and control of gene expression. Many k-turns are binding sites for proteins, such as the L7Ae protein.

In the absence of metal ions, the k-turn adopts a less-tightly kinked structure, but can be induced to fold into its kinked conformation by the addition of metal ions or binding proteins. This provides a simple system for the study of RNA folding, readily followed by fluorescence resonance energy transfer, where the final structure is known for several k-turns. The role of hydrogen bonding in stabilizing the folded conformation has been dissected in detail.

The induction of the folded structure is a good example of induced fit. Proteins such as L7Ae bind with extremely high affinity, stabilizing the kinked structure.

Tertiary structure can also assist the folding process. A number of riboswitches contain k-turns; for example the SAM riboswich contains a k-turn that facilitates the formation of a loop-loop interaction. If the k-turn is disrupted, the riboswich can no longer bind SAM. However, the tertiary structure forces the folding of sub-optimal k-turns that are incapable of folding alone. We have determined the crystal structure of the forced structure, showing the presence of all the key interactions despite the absence of a normally-essential G•A basepair. ITC measurements show the altered riboswitch binds SAM.

We have created a web-based database of k-turn structures, which can be found at http://www.dundee.ac.uk/biocentre/nasg/kturn/ .

Cynthia Therese McMurray

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Education:

1983 B.S. Florida State University
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1990 Postdoc Vollum Institute

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1999-Present: Professor of Biochemistry and Pharmacology, Mayo Clinic, Rochester, MN
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Cynthia McMurray has been the PI on multiple NIH grants, and has served on the executive board and staff review board at the Mayo Clinic before her arrival at LBNL last year. There, she received the Distinguished Investigator ward with a prize of 500K for her research. She has long-standing interest and expertise in mitochondria, vesicle trafficking and lipid metabolism. She has extensive experience in evaluating the pathophysiology of Huntington's disease, and mechanisms for trinucleotide expansion, underlying a number of severe neurodegenerative diseases. She has worked for over 15 years on the neuropathology of Huntington's disease (HD) using mouse models, and in developing therapeutics. She has discovered that the caveolar pathway of vesicle trafficking is involved in HD.

AWARDS, HONORS AND PROFESSIONAL MEMBERSHIPS

Editorial Board, *J. Biological Chemistry*
2001 Distinguished Mayo Investigator & Prize
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Selected Publications:

1. Kovtun IV, and McMurray CT. (2008) Mechanisms of Triplet Repeats expansions *in vivo*, Cell Res. 2008 (January) 198-213.
2. Rolseth V, Rundén-Pran E, Luna L, **McMurray CT**, Bjørås M, Ottersen OP. Widespread distribution of DNA glycosylases removing oxidative DNA lesions in human and rodent brains. DNA Repair (Amst). 7(9), 1578-88 (2008).
3. Owen BA, Lang WH, **McMurray CT**. The nucleotide binding dynamics of human MSH2-MSH3 are lesion dependent. (2009) Nature Structural and Molecular Biology 16, 550-7 (2009). NIHMSID: NIHMS238465. PMC Journal – In Process.
4. Trushina E, Rana S, **McMurray CT**, and Duy H. Tricyclic pyrone compounds prevent aggregation and reverse cellular phenotypes caused by expression of mutant huntingtin protein in striatal neurons. BMC Neuroscience 10:73. (2009). PMCID: PMC2719645.
5. **McMurray CT** (2010). Mechanisms of DNA expansion during human development. Nature Rev Genet. 11(11), 786-99 (2010).
6. Trushina E and **McMurray CT** (2010). Loss of Caveolin-1 in Huntington's disease Mice Suppresses Pathophysiology in vivo. Nature Neuroscience, in revision.

CONFORMATIONAL TRAPPING OF MSH2/MSH3 ON REPAIR RESISTANT DNA LOOPS

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The mechanism by which repair-resistant loops in DNA become insertion and deletion mutations is unknown. Here, we address the underlying basis for discriminating repair competent and repair resistant DNA loops by MSH2/MSH3. We find that MSH2/MSH3 binds with similar affinity to a repair competent $(CA)_4$ loop and to repair-resistant CAG hairpins. However, the 3-way hairpin junction shows a conformational state that traps nucleotide-bound MSH2/MSH3, and inhibits its dissociation from the hairpin. The biochemical and smFRET results imply that, at repair-resistant CAG hairpins, the novel DNA conformation provides a non-productive binding site for nucleotide-bound MSH2/MSH3, which fails to effectively couple DNA binding with downstream repair signaling, We envision that conformational regulation of small loop repair occurs at the level of the junction dynamics.

Yingfu Li

Yingfu Li received his BSc in Chemistry from Anhui University, China, in 1983, and his MSc in organic synthesis in China Agriculture University in 1986. He obtained his PhD from Simon Fraser University, Canada, in 1997 under the guidance of Prof. Dipankar Sen. He spent the next two years at Yale University as a postdoctoral fellow with Prof. Ronald Breaker. In 1999 he joined McMaster University as an Assistant Professor in the Department of Biochemistry and Biomedical Sciences and the Department of Chemistry and Chemical Biology. He is now a Professor and a Canada Research Chair in Nucleic Acids Research at McMaster University. His research interests include DNAzymes, aptamers, biosensors, nanotechnology, bacterial toxins and non-coding RNAs.

Sequence-toxicity relationship of IbsC, a type I toxin in Escherichia coli

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Bacterial genomes encode a collection of small peptides that are deleterious to their hosts when overexpressed. The physiological relevance of the majority of these peptides is unknown at present, although many of them have been implicated in regulatory processes important for cell survival and adaptability. One peptide that is of particular interest to us is a 19 amino acid proteic toxin, coined IbsC, whose production is repressed by SibC, an RNA antitoxin. Together, IbsC and SibC constitute a type I toxin-antitoxin (TA) pair. To better understand the function of IbsC and to decipher the sequence determinants for its toxic phenotype, we carried out extensive sequence analyses of the peptide. We generated a series of truncation and single amino acid deletion mutants to determine the minimal sequence required for toxicity. We further probed into functionally-relevant amino acids with a comprehensive set of IbsC mutants produced using a systematic sequence randomization strategy. We found that IbsC remained toxic in the presence of multiple deletions and single amino acid substitutions, despite being well-conserved in E. coli and across other Gram-negative bacteria. The toxicity of this peptide was determined to be dependent on a stretch of highly hydrophobic residues near its center. Our results defined sequence-function relationship of IbsC and offered additional insights into properties common to membrane-targeting type I toxins in E. coli and related species.

Thomas A. Steitz

Dr. Thomas A. Steitz is Sterling Professor of Molecular Biophysics and Biochemistry and Professor of Chemistry at Yale University as well as an Investigator of the Howard Hughes Medical Institute. He received a B.A. degree in chemistry from Lawrence College in Appleton, Wisconsin, and a Ph.D. degree in molecular biology and biochemistry from Harvard. After a postdoctoral year at Harvard, he moved to the Medical Research Council Laboratory of Molecular Biology in Cambridge, England, to work as a Jane Coffin Childs Fellow. He next joined the Yale faculty, where he has remained, except for sabbatical work in Göttingen, Germany, Cambridge, England, the California Institute of Technology and the University of Colorado. He is a member of the U.S. National Academy of Sciences and the American Academy of Arts and Sciences. He has received the Pfizer prize from the American Chemical Society, the Rosenstiel Award for distinguished work in basic biomedical sciences, the AAAS Newcomb Cleveland Prize, the Keio Medical Science Prize, the Gairdner International Award and the 2009 Nobel Prize in Chemistry.

For the last three decades, research in the laboratory of Dr. Steitz has focused on obtaining insights into the molecular mechanisms by which the proteins and nucleic acids involved in the central dogma of molecular biology carry out gene expression from replication and recombination of the DNA genome to its transcription into mRNA followed by the various components associated with the translation of mRNA into protein. Not only are these processes fundamental to all life forms, but many of the macromolecules involved in these processes are known, or potential, targets for therapeutic drugs. In the 1980s, his lab established the structure to the catabolite gene activator protein and later its DNA complex, the structure of the first DNA polymerase and the first structure of an aminoacyl tRNA synthetase bound to tRNA. His studies of T7 RNA polymerase captured in many of its functionally important states - initiation, intermediate, elongation - as well as stages of nucleotide incorporation and provide the most complete picture of RNA transcription by RNA polymerase. Perhaps the most significant insights have been derived from the atomic structure of the large ribosomal subunit. This structure proved that the ribosomal RNA is entirely responsible for catalyzing peptide bond formation and provided insights into how this mammoth RNA assembly is folded and functions as an enzyme. The large ribosomal subunit is probably the major target of antibiotics that are effective pharmaceuticals. The many structures of the large subunit complexed with various different antibiotics determined at Yale have identified numerous different antibiotic binding sites near the site of protein synthesis. This information has been enormously facilitating in the development of new antibiotics that will be effective against the rapidly increasing number of antibiotic resistant bacteria. Rib-X Pharmaceuticals, Inc. in New Haven has used this structural information to develop one compound that has successfully completed phase II clinical trials and a second that should enter clinical trials shortly.

From the Structure and Function of the Ribosome to New Antibiotics

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We have obtained many insights into the structural basis of ribosome function in protein synthesis from our structural studies of the 50S and 70S bacterial ribosomes and their complexes with substrates. The ribosome is a very major target of antibiotics and the crystal structures of either the large or small ribosomal subunits or the 70S ribosome complexed with antibiotics from various families have led to an understanding of the mechanisms by which they are able to inhibit protein synthesis. Further, they have facilitated the understanding of the mechanisms of antibiotic resistance, and they have enabled the use of structure based drug design to obtain compounds that are effective against medically important antibiotic resistant bacterial strains. The structures of some of our antibiotic complexes have been used by Rib-X Pharmaceuticals, Inc. of New Haven to develop new potential antibiotic compounds that are effective against MRSA, one of which has successfully completed phase II clinical trials. Recently, we have determined the crystal structures of the 70S ribosome bound to two compounds that are effective against TB, capreomycin and viomycin. Since their binding site is adjacent to those of two antibiotics that bind to the small subunit, the design of new anti-TB antibiotics by chemically combining components of the neighboring compounds should be possible.

Zihe Rao (饶子和)

Zihe Rao is a molecular biophysicist and structural biologist. A graduate of the University of Science and Technology of China (USTC), he received his Master's degree from the Graduate School of the Chinese Academy of Sciences and his doctoral degree from the University of Melbourne, Australia.

Following a long period of research in the University of Oxford, he returned to China as a Professor of Structural Biology in Tsinghua University.

Zihe Rao is mainly engaged in the study of the three-dimensional structures of significant proteins related to human disease or with important physiological functions, as well as in innovative drug discovery. He has published more than 200 peer-reviewed papers to date in international scientific journals.

Zihe Rao was elected as a Member of the Chinese Academy of Sciences in 2003, a Member of the Third World Academy of Sciences in 2004 and a Fellow of Hertford College, Oxford, in 2011.

Structure and function of the coronavirus replication and transcription machinery

Zihe Rao

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Coronaviruses, including SARS coronavirus, mouse hepatitis virus (MHV) and several human coronaviruses (HCoV), belong to a large virus family and are implicated in severe human and animal diseases. The coronaviruses are positive-strand RNA viruses that utilize the host ribosome to translate proteins for their replication and transcription machinery immediately following viral entry. This process uses the viral genomic RNA as a template to generate several polypeptides, which are then self-processed into fifteen or sixteen non-structural proteins (NSP) that perform specific functions within the replication and transcription centre (RTC) of the virus. The key components of the RTC include nsp2, nsp4, nsp5 (main protease), nsp7-8 (primase, or secondary polymerase), nsp10, nsp12 (RdRP), nsp13 (helicase), nsp14 (3'-to-5' exonuclease, (guanine-N7)-methyltransferase), nsp15 (uridylate-specific endoribonuclease), and nsp16 (2'-O-ribose methyltransferase). Understanding their structure, function and assembly within the RTC is crucial for elucidation of the precise molecular mechanism of coronavirus replication and transcription, and will provide a structural basis for anti-viral drug discovery in order to combat the threat posed by coronaviruses.

Chuan He (何川)

Chuan He, Ph.D., is a professor in the Department of Chemistry and Institute for Biophysical Dynamics at the University of Chicago, and a Cheung Kong Professor in the Department of Chemical Biology at Peking University. He received his B.S. (1994) from the University of Science and Technology of China and his Ph. D. degree from Massachusetts Institute of Technology in chemistry in 2000. After being trained as a Damon-Runyon postdoctoral fellow at Harvard University from 2000-2002, he joined the University of Chicago as an assistant professor in the Department of Chemistry and was promoted to full professor in 2010. He is also a member of the Institute for Biophysical Dynamics and Cancer Research Center at the University of Chicago. His research spans a broad range of chemistry, chemical biology, microbiology, biochemistry, structural biology and cell biology.

Oxidative RNA Modification and De-Modification — Towards RNA Epigenetics

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The five bases that comprise nucleic acids─ adenine, guanine, cytosine, thymine, and uracil ─ can be chemically and enzymatically modified. These modification and de-modification events can have significant biological consequences, particularly for gene expression. The AlkB family dioxygenases are newly discovered proteins that use a novel oxidative demethylation process to remove a methyl group from DNA/RNA bases. The prototype, the *E. coli* AlkB, is a DNA/RNA base damage repair enzyme that catalyzes direct reversal of N1-methyladenine (1-meA), N3-methylcytosine (3-meC), and exocyclic DNA base lesions. Nine sequence homologues have been identified in the human genome. Some of these proteins play critical roles in obesity/diabetes and various cancers. I will present our recent results that reveal the exact biological substrates and cellular function of some of these intriguing enzymes. Based on these discoveries we propose a new mode of biological regulation that depends on reversible RNA modification, for which we termed “RNA Epigenetics”.

Lee, Hon Cheung (李汉璋)

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Academic Qualifications and Positions Held:

Chair Professor and Head: 2006-present, Department of Physiology, University of Hong Kong.

Professor:1999-2006, Department of Pharmacology, University of Minnesota, Minneapolis, USA.

Assistant Professor to Full Professor: 1981-1999, Department of Physiology, University of Minnesota, Minneapolis, USA.

B.A.(1971); M.S.(1973) in Physics and Ph.D.(1978) in Biophysics; all degrees from University of California at Berkeley, USA.

Honors and other professional activities (1994-present).

Academy for Excellence in Health Research, University of Minnesota, permanently inducted in 2004.

Editorial Board, Journal of Biological Chemistry, 2003-2008.

Honorary degree in Medicine and Surgery, University of Genoa, Italy, 1997.

Distinguished McKnight University Professor, University of Minnesota, 1996-2006.

Keynote Lecture, FASEB Research Conference on "NAD Metabolism & Signaling", Lucca, Italy, 2011. Nishizuka Lecture, 17th Symposium on Ca2+-Binding Proteins and Ca2+ Function. Beijing, China, 2011.

Plenary Lecturer, Korean Society of Medical Biochemistry and Molecular Biology, Seoul, Korea, 2008.

Plenary Lecture, Scandinavian Congress of Physiology, Odense, Denmark, 2003.

Starting Lecture, British Physiological Society Meeting, London, UK, 2002.

Keynote Lecture, Pharmacological Society of Japan, Sapporo, Japan, 1999.

Keynote Lecture, FASEB Summer Research Conference on CD38, Vermont, USA, 1998.

Keynote Speaker, 3rd International CD38 Workshop, Paris, France, 1997.

Eraldo Antonini Lecture, National Biochemical Society, Pavia, Italy, 1994.

Representative Publications (Articles:144; Total citations: 9,366; h-index: 52, ISI):

1. Clapper, D.L., Walseth, T.F., Dargie, P.J. and Lee, H.C. (1987) Pyridine nucleotide metabolites stimulate calcium release from sea urchin egg microsomes desensitized to inositol trisphosphate. J. Biol. Chem. 262, 9561-9568. Citations: 378.
2. Lee, H.C., Walseth, T.F., Bratt, G.T., Hayes, R.N., and Clapper, D.L. (1989) Structural determination of a cyclic metabolite of NAD+ with intracellular Ca+2 mobilizing activity. J. Biol. Chem. 264, 1608-1615. Citations: 374.
3. Lee, H.C. and Aarhus, R (1991) ADP-ribosyl cyclase: an enzyme that cyclizes NAD+ into a calcium-mobilizing metabolite. Cell Regulation 2, 203-209. Citations: 257. Galione, A., Lee, H.C. and Busa, W.B. (1991) Ca+2 -induced Ca+2 release in sea urchin egg homogenates and its modulation by cyclic ADP-ribose. Science 253, 1143-1146. Citations: 491.
4. Lee, H.C., Aarhus, R. and Walseth, T.F. (1993) Calcium mobilization by dual receptors during fertilization of sea urchin eggs. Science 261, 352-355. Citations: 252.
5. Howard, M., Grimaldi, J.C., Bazan, J.F., Lund, F.E., Santos-Argumedo, L., Parkhouse, R.M.E., Walseth, T.F. and Lee, H.C. (1993) Formation and hydrolysis of cyclic ADP-ribose catalyzed by lymphocyte antigen CD38. Science 262, 1056-1059. Citations: 468.
6. Lee, H.C., Aarhus, R., Graeff, R., Gurnack, M.E. and Walseth, T.F. (1994) Cyclic ADP-ribose activation of the ryanodine receptor is mediated by calmodulin. Nature 370, 307-309. Citations: 184.
7. Graeff, R., Liu, Q., Kriksunov, I.A., Kotaka, M., Oppenheimer, N., Hao, Q. and Lee, H.C. (2009) Mechanism of cyclizing NAD to cyclic ADP-ribose by ADP-ribosyl cyclase and CD38. J. Biol. Chem. 284, 27629–27636.

Selected as top 1% of papers in JBC and featured on the journal cover.

CD38 – A Novel Calcium Signalling Enzyme and a Target for Drug Design

李汉璋 (Lee, Hon Cheung)

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CD38 is a trans-membrane protein ubiquitously expressed in virtually all mammalian tissues. It was originally identified as a lymphocyte antigen with unknown function by antibody typing. Our interest in CD38 derived from our investigations on Ca^{2+}-signalling that had led to the discovery of two novel second messenger molecules for mobilizing the intracellular stores, cyclic ADP-ribose (cADPR), a cyclic nucleotide derived from NAD, and nicotinic acid adenine dinucleotide phosphate (NAADP), a linear metabolite of NADP. The messenger functions of both cADPR and NAADP have now been well documented in a wide range of cellular systems covering three biological kingdoms. Two decades of work by us and others has since established that CD38 is a novel Ca^{2+}-signalling enzyme responsible synthesizing both cADPR and NAADP. Gene knockout studies in mice have confirmed the critical roles of CD38 in a wide range of physiological functions from insulin secretion, bone resorption, susceptibility to bacterial infection, to social behaviour of mice through modulating neuronal oxytocin secretion. Its physiological importance has made CD38 a concerted target for drug design. We have elucidated the catalytic mechanism of CD38 to atomic resolution by X-ray crystallography and site-directed mutagenesis. This presentation will give a brief account of the discovery of the Ca^{2+} signalling functions of CD38 and describe the current effort in designing specific inhibitors for this novel Ca^{2+} signalling enzyme.

Zhen Huang (黄震)

Zhen Huang was born in 1964 and raised in Sichuan, China. He received his B.S. degree from Sichuan University in 1984 (under the supervision of Professor Shulin Chen), M.S. from Peking University in 1987 (under the supervision of Professor Wen Zhong), and Ph.D. degree from Swiss Federal Institute of Technology (ETH, Zurich) in 1994 (under the supervision of Professor Steven Benner). In 1994, he joined the Department of Genetics at Harvard Medical School as a research fellow, in Laboratory of Professor Jack Szostak (Nobel Laureate in Medicine in 2009). He was hired in 1998 by Brooklyn College, City University of New York, as assistant professor and was later promoted to associate professor with tenure. In 2004, Dr. Huang was recruited to Chemistry Department, Georgia State University, is Professor of Chemistry and Chemical Biology, and is also Distinguished Professor Awardee of Georgia State University. He has received several awards, and 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 pioneered and has developed selenium and tellurium derivatizations of nucleic acids for structure and function studies of nucleic acids and protein-nucleic acid complexes. His current research interests are in selenium and tellurium derivatizations of DNAs and RNAs for X-ray crystallographic studies of nucleic acids and protein complexes, synthesis of analogs of nucleosides and nucleotides for structure, function and therapeutic studies, development of RNA microchip technology for direct detection and quantitation of gene expression profile, 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 and CDC, state funding agencies, the distinguished cancer scholar award, and private fundings (such as industries). He has received several US patents, and many US and international patents are pending.

Chemical and Structural Biology of Selenium- and Tellurium-Nucleic Acids for Novel Drug Discovery

Jia Sheng, Jozef Salon, Jianhua Gan, Julianne Caton-Williams, Abdalla Hassan, Wen Zhang, ***Zhen Huang****,* Department of Chemistry & Department of Biology, Georgia State University, Atlanta, GA 30303, USA, Huang@gsu.edu*

3D structure determination and study of nucleic acids and protein-nucleic acid complexes have enormous importance for disease molecular mechanism research and drug discovery. X-ray crystallography is one of the most direct and powerful tools for structure determination of these macromolecules and complexes. Via chemogenetic and chemical synthetic strategies, recently my laboratory pioneered and has developed atom-specific substitution of nucleic acid oxygen with selenium and tellurium [Se-derivatized nucleic acids (SeNA) and Te-derivatized nucleic acids (TeNA); Ref. 1-8], which can be used as atomic probes for structure and function studies of nucleic acids. As oxygen, selenium and tellurium are in the same elemental group in the periodic table, the atom-specific mutagenesis by replacing nucleotide oxygen with selenium or tellurium can reveal novel chemistry, structure, function and mechanism of nucleic acids, such as non-coding RNAs, including hammerhead ribozymes, siRNAs and microRNAs. Moreover, the Se derivatization and the atom-specific substitution lead to a novel paradigm of nucleic acids and allow discoveries of new applications and materials, such as self-assembling nano and molecular electronic materials. Our nucleic acid chemogenetic strategy with selenium, without causing structural perturbation, has demonstrated great potentials as a general methodology for structure and function studies of nucleic acids as well as their protein complexes. Furthermore, we found that the Se-derivatization can facilitate crystallization and the diffraction quality is high. Excitingly, we have also recently determined the first nucleic acid-protein complex via the nucleic acid Se-derivatization and the MAD phasing.

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Selected Publications:

1. Jia Sheng, Abdalla E. A. Hassan, Wen Zhang, Jianfeng Zhou, Bingqian Xu, Alexei S. Soares and Zhen Huang*, "Synthesis, Structure and Imaging of Oligodeoxyribonucleotides with Tellurium-nucleobase Derivatization", *Nucleic Acids Research*, **2011**, *39*, 3962-3971.
2. Wen Zhang and Zhen Huang*, "Synthesis of the 5'-Se-Thymidine Phosphoramidite and Convenient Labeling of DNA Oligonucleotide", *Organic Letter*, **2011**, 13, 2000-2003.
3. Julianne Caton-Williams, Lina Lin, Mathew Smith, and Zhen Huang*, "Convenient Synthesis of Nucleoside 5'-Triphosphates for RNA Transcription", *Chemical Communications*, **2011**, in press.
4. Lina Lin, Jia Sheng, Zhen Huang*, "Nucleic Acid X-ray Crystallography via Direct Selenium Derivatization", *Chemical Society Reviews* (invited and peer reviewed), **2011**, in press.
5. Abdalla E. A. Hassan, Jia Sheng, Wen Zhang, and Zhen Huang*, "High Fidelity of Base Paring by 2-Selenothymidine in DNA", *Journal of American Chemical Society*, **2010**, *132*, 2120-2121.
6. Sheng, Salon, Gan, Huang*, "Synthesis and Crystal Structure Study of 2'-Se-Adenosine-Derivatized DNA", *Science China: Chemistry*, **2010**, 53, 78-85.
7. Salon, Sheng, Gan, Huang*, "Synthesis and crystal structure of 2'-Se-modified guanosine containing DNA", *J. Org. Chem.,* **2010**, 75, 637-641.
8. Jia Sheng and Zhen Huang*, "Selenium Derivatization of Nucleic Acids for X-ray Crystal Structure and Function Studies", (invited and peer reviewed), *Chemistry and Biodiversity* (John Wiley & Sons, Inc.), **2010**, *7*, 753-785.

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Haitao Li is currently a professor at the Center for Structural Biology, School of Life Sciences and School of Medicine, Tsinghua University. He received his Ph.D. in molecular biophysics from the Institute of Biophysics, CAS, Beijing, in 2003. Then he joined Dinshaw J. Patel laboratory at the Memorial Sloan-Kettering Cancer Center at New York to carry out his postdoctoral research. In 2006, he was prompted as Senior Research Scientist at the Patel laboratory. In 2010, he joined Tsinghua Medical School as full-time faculty member. Dr. Li's laboratory at Tsinghua focuses on the structural biology of epigenetic regulation impacting on human disease and stem cell biology, with an ultimate goal for structure-based new drug discovery. His current research interests include 1) site- and state-specific recognition and regulation of the 'histone code'; 2) structure and function of the BAZ-family chromatin remodeling complexes; and 3) non-coding RNA-mediated heterochromatin formation.

Selected publications:

1. Iwase S, Xiang B, Ghosh S, Ren T, Lewis PW, Cochrane JC, Allis CD, Picketts DJ, Patel DJ*, Li H*, Shi Y* (2011) ATRX links atypical histone methylation recognition mechanisms to human mental retardation syndrome**.** ***Nat Struct Mol Biol*** (in press) (*co-correspondance)
2. Ruthenburg AJ, Li H, Milne T, Dou Y, McGinty RK, Yuen M, Muir TW, Patel DJ and Allis CD (2011) Multivalent interactions interpret the histone at the nucleosome level. ***Cell*** (in press)
3. Wang Y, Juranek S, Li H, Sheng G, Greg SW, Tuschl T and Patel DJ (2009) Nucleation, propagation and cleavage of target RNAs in argonaute silencing complexes. ***Nature*** 461:754-61
4. Li H*, Motamedi MR*, Yip CK, Wang Z, Walz T, Patel DJ and Moazed D (2009) An alpha motif at Tas3 C terminus mediates RITS cis-spreading and promotes heterochromatic gene silencing. ***Mol Cell*** 34(2), 155-167 (*equal contribution)
5. Xiao A, Li H, Shechter D, Ahn SH, Fabrizio LA, Erdjument-Bromage H, Ishibe-Murakami S, Wang B, Tempst P, Hofmann K, Patel DJ, Elledge SJ and Allis CD. (2009) WSTF regulates the DNA damage response of H2A.X via a novel tyrosine kinase activity. ***Nature*** 457, 57-62
6. Wang Y, Juranek S, Li H, Sheng G, Tuschl T and Patel DJ (2008) Structure of an argonaute silencing complex with a seed-containing guide DNA and target RNA duplex. ***Nature*** 456, 921-926
7. Ruthenburg AJ, Li H, Patel DJ, and Allis CD. (2007) Multivalent engagement of chromatin modifications by linked binding modules. ***Nat Rev Mol Cell Biol*** 8(12):983-994
8. Taverna SD*, Li H*, Ruthenburg AJ, Allis CD, and Patel DJ* (2007) How chromatin-binding modules interpret histone modifications: lessons from professional pocket pickers. ***Nat Struct Mol Biol*** 14(11):1025-1040 (*equal contribution & co-correspondance)
9. Li H, Fischle W, Wang W, Duncan EM, Liang L, Murakami-Ishibe S, Allis CD, and Patel DJ (2007) Structural basis for lower lysine methylation state-specific readout by MBT repeats of L3MBTL1 and an engineered PHD finger. ***Mol Cell*** 28(4), 677-691
10. Li H, Ilin S, Wang W, Duncan EM, Wysocka J, Allis, CD, and Patel DJ (2006) Molecular basis for site-specific readout of histone H3K4me3 trimethylation by the BPTF PHD finger of NURF. ***Nature***

Atypical and combinatorial readout of histone methylation by ATRX ADD domain

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ATR-X (alpha thalassemia/mental retardation, X-linked) syndrome is a human congenital disorder that causes severe intellectual disabilities in male children. Mutations in the ATRX gene, which encodes an ATP-dependent chromatin-remodeling enzyme, are responsible for the syndrome. Approximately 50% of human missense mutations are clustered in a conserved cysteine-rich domain of ATRX, termed ADD (ATRX-DNMT3-DNMT3L, ADD_{ATRX}), indicating its importance. Here we report the identification of ADD_{ATRX} as a novel histone H3K9me3 reader module, whose efficient H3 binding requires a combinatorial pattern of trimethylated K9 and unmethylated K4. The atomic resolution co-crystal structure of ADD_{ATRX} bound to H3K9me3 peptide reveals an atypical composite binding pocket, rich in polar residues and positioned at the interface between the GATA and PHD fingers of ADD_{ATRX}, which accommodates the trimethylated K9 residue in a mode distinctive from the conventional trimethyllysine-binding aromatic cage. Importantly, binding of ADD_{ATRX} to H3K9me3 is critical for ATRX pericentromeric heterochromatin localization *in vivo*, which is disrupted by patient mutations in ADD_{ATRX}. In addition, we observed strong inhibitory effects of H3T6 phosphorylation on ADD_{ATRX} binding to H3K9me3, while H3S10 phosphorylation was shown to be tolerable, suggesting possible modification crosstalks. Taken together, we have discovered and provided structural insights into a unique histone recognition mechanism that is compromised in a human intellectual and developmental disorder, thus shedding new light on the molecular mechanism underlying ATR-X etiology.

Xin-Shan Ye (叶新山)

Dr. Xin-Shan Ye is Professor of Medicinal Chemistry at Peking University. He received his B.S. and M.S. degrees from Wuhan University in Central China in 1985 and in 1988, respectively. He was appointed as a lecturer at Huazhong Agricultural University in Wuhan from 1988 to 1993. Then he spent three years in Hong Kong for his doctoral study and obtained his Ph.D. degree from The Chinese University of Hong Kong in 1996 under the direction of Prof. Henry Wong. After three and a half years of post-doctoral research with Prof. Chi-Huey Wong at The Scripps Research Institute, he went back to China in 2000 and was appointed as Changjiang Professor at Peking University. Now he is the director of the State Key Laboratory of Natural and Biomimetic Drugs. He serves on the editorial board of international journal Carbohydrate Research.

The research of the Ye group deals with chemical glycobiology and carbohydrate-based drug discovery. The research interests include the development of new methodologies or strategies for the assembly of oligosaccharides, the synthesis and evaluation of biologically important oligosaccharides such as tumor-associated antigens, as well as the design, synthesis and evaluation of carbohydrate-processing enzyme inhibitors.

Dr. Xin-Shan Ye has published more than 60 scientific papers in international peer-reviewed journals. He received the National Outstanding Young Investigator award by Natural Science Foundation of China in 2005.

Chemical Modifications of Aminoglycoside Antibiotics Targeting RNA

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The increased awareness of the central role of RNA has led to the realization that RNA, as structural and functional information accumulation, is also drug target to small molecular therapy. Aminoglycosides are a group of well-known antibiotics, which function through binding to specific sites in prokaryotic ribosomal RNA (rRNA) and affecting the fidelity of protein synthesis. Unfortunately, their clinical practice has been curtailed by toxicity and rapid increasing number of resistant strains. Therefore, it is highly desirable to design new modified aminoglycosides that will overcome the undesirable properties of natural occurring aminoglycosides. Herein we report our efforts to find new aminoglycoside derivatives based on modifications of aminoglycoside antibiotics.

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Education:

1995 -1998 Ph.D. Institute of Biophysics, Chinese Academy of Sciences, Beijing, China.

1987-1991 B.S. Chemistry department, Xiamen University , Fujian, China

Professional Experience:

2004-present Professor, National Laboratory of Biomacromolecules, Institute of Biophysics, Chinese Academy of Sciences.

1999--2004 Associate professor, National Laboratory of Biomacromolecules, Institute of Biophysics, Chinese Academy of Sciences.

1991-1998 Staff, National Laboratory of Biomacromolecules, Institute of Biophysics, Chinese Academy of Sciences

Selected Publications:

1. Tang, L., Bai, L, Wang, W.H., **Jiang, T.*** Crystal Structure of the Carnitine Transporter and Insights into the Antiport Mechanism. ***Nat. Struct. Mol. Biol.*** 17(4), 492-496 (2010).
2. Xu, M., Bai, L., Xie, W., Gong, Y., Hang, H.Y. * **Jiang, T.*** Structure and Functional Implications of the Human Rad9-Hus1-Rad1 Cell Cycle Checkpoint Complex. ***J. Biol. Chem.*** **284** , 20457-20461 (2009).
3. Gong,Y., Cao, P., Yu, H.J., **Jiang, T.*** Crystal structure of the neurotrophin-3 and p75 NTR symmetrical complex. ***Nature*** **454** ,789-793(2008).
4. Zhou, Q., Wang, Q.L., Meng, X., Strauss, J., Shu, Y., **Jiang, T.**, Wagenknecht, T., Yin, C.C., Sui, S.F., Liu, Z. Structural and Functional Characterization of Ryanodine Receptor-Natrin Toxin Interaction. ***Biophys J.*** **95**, 4289-99(2008).
5. Liu, S.Q., Wang, F, Tang, L, Gui, W.J. , Cao, P , Liu, X.Q., Poon, W.S., Shaw, P.C.* , **Jiang, T.*** Crystal structure of mastoparan from *Polistes jadwagae* at 1.2 angstrom resolution. ***J. Struct. Biol.*** **160**, 28-34(2007).
6. Cao, P., Gong, Y., Tang, L., Leung, Y.C., **Jiang, T.*** Crystal structure of human pyridoxal kinase. ***J. Struct. Biol.*** **154**, 327-32(2006).
7. Wang, F., Li H, Liu MN, Song H, Han HM, Wang QL, Yin CC, Zhou YC, Qi Z, Shu YY, Lin ZJ, **Jiang T.*** Structural and functional analysis of natrin, a venom protein that targets various ion channels. ***Biochem. Biophys. Res. Commun.*** **351**, 443-8(2006).
8. Wang, F., Liu, X.Q., Li, H., Liang, K.N., Miner, J.N., Hong, M., Kallel, E.A., Oeveren, A.V., Zhi, L., **Jiang, T.*** Structure of ligand-binding domain(LBD)of human androgen receptor in complex with a selective modularor LGD2226. ***Acta Cryst. F62,*** 1067-1071(2006).
9. Wang, F., Liu, X.Q., Li, H., Lang, X.J., Peng, H., Liu, S.Q., **Jiang, T.*** Crystallization and Preliminary X-Ray Diffraction Analysis of Three Mastoparans. ***Protein & Peptide Letters*** **13**,629-631(2006).

Crystal structure of rad9-hus1-rad1 cell cycle checkpoint complex

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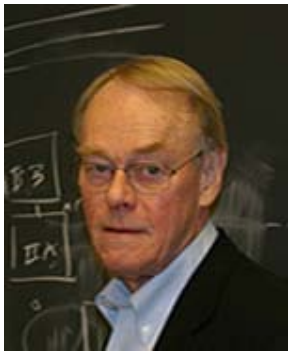
Cellular DNA lesions are efficiently countered by DNA repair in conjunction with delays in cell-cycle progression. Previous studies have demonstrated that Rad9, Hus1, and Rad1 form a heterotrimeric complex (the 9-1-1 complex) that plays dual roles in cell cycle checkpoint activation and DNA repair in eukaryotic cells. Here we report the crystal structure of the human 9-1-1 complex at 3.2Å resolution. The crystal structure, together with biochemical assays, reveals that the interdomain connecting (IDC) loops of Rad9, Hus1, and Rad1 are largely divergent, and further crystallographic study indicates that a PCNA-interacting-box (PIP-box) containing peptide derived from Fen1 binds tightly to the IDC loop of Rad1.Moreover, structural and biochemical analysis reveal that the Rad17-RFC2-5 clamp loader loads the 9-1-1 clamp onto DNA via the interaction between Rad17 and Rad1 by opening the Rad1-Rad9 interface. Furthermore, structural comparison with PCNA reveals other unique structural features of the 9-1-1 complex (the αII1-βII2 loop in Rad9 and the αI2-βI7 loop in Rad1) that are proposed to contribute to DNA damage recognition. Taken together, we provide a DNA damage sensing model of the 9-1-1 complex.

Wayne A. Hendrickson



Wayne A. Hendrickson is a University Professor at Columbia University and an Investigator with the Howard Hughes Medical Institute (HHMI). He has a B.A. from the University of Wisconsin at River Falls and a Ph.D. in biophysics from Johns Hopkins University based on work with Warner Love. His postdoctoral research was with Jerome Karle at the Naval Research Laboratory (NRL). He remained at NRL as a Research Biophysicist until 1984 when he joined the Department of Biochemistry and Molecular Biophysics at Columbia. In 1986, Hendrickson became an HHMI Investigator; in 2008, he was named the Violin Family Professor of Physiology and Cellular Biophysics; in 2009, he joined the National Synchrotron Light Source – II (NSLS-II) project at Brookhaven National Laboratory where he is now Chief Life Scientist; and in 2010, he became the Scientific Director of the New York Structural Biology Center.

Research in Dr. Hendrickson's laboratory focuses on the structure and function of biological molecules. He and his colleagues use x-ray crystallography to study molecular properties in atomic detail. By analyzing x-ray beams diffracted from crystals, they are able to reconstruct images of crystallized molecules. Their advances in diffraction methods (notably, stereochemically restrained refinement, the multiwavelength-anomalous-diffraction (MAD) method, selenomethionyl proteins, and synchrotron instrumentation) have been instrumental in the emergence of structural biology as a major force in modern biology and molecular medicine. They use this technology themselves in investigations on membrane receptors and cellular signaling, on viral proteins and HIV infection, on molecular chaperones and protein folding, and in structural genomics of membrane proteins.

Dr. Hendrickson has published numerous research articles and related reviews. He serves on advisory bodies for various scientific organizations. He is a founding editor of *Current Opinion in Structural Biology* and of *Structure*, and he was a founder of SGX Pharmaceuticals. His honors include the Aminoff Prize of the Royal Swedish Academy of Sciences, the Gairdner International Award, and the Harvey Prize of the Technion – Israel Institute of Technology. He is a fellow of the American Academy of Arts and Sciences and a member of the National Academy of Sciences.

Seeing How Membrane Channels and Transporters Work

Wayne Hendrickson

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The New York Consortium on Membrane Protein Structure (NYCOMPS) is taking a structural genomics approach to enable biological discovery and to enhance structural coverage for the universe of membrane proteins. Several recently obtained NYCOMPS structures have proven on functional testing to be channels or transporters. Significant biological insight derives from structure-inspired hypotheses generated in these studies, and understanding of biophysical principles develops from structural novelty obtained. I will summarize the results from several of these structures and focus in greater depth on an anion channel that we study. The SLAC1 anion channel controls turgor pressure in the aperture-defining guard cells of plant stomata, thereby regulating the exchange of water vapor and photosynthetic gases in response to environmental signals such as drought or high levels of carbon dioxide. We obtained the crystal structure of a bacterial homolog of SLAC1 at 1.20 Å resolution, and then used structure-inspired mutagenesis to analyze structural and ion conductance properties of this bacterial protein and of the related plant SLAC1 channels.

Peixuan Guo (郭培宣)

Endowed Chair in Biomedical Engineering at University of Cincinnati since 1987; Director of NIH/NCI Cancer Nanotech Platform Partnerships for RNA Nanotechnology in Cancer Therapy since 2010; director of one NIH Nanomedicine Development Center from 2006 to 2011. Ph.D, University of Minnesota in 1987. After postdoctoral at NIH, he joined Purdue University in 1990, tenured in 1993, full Professor in 1997, and honored as Purdue Faculty Scholar in 1998. He constructed phi29 DNA packaging motor (*PNAS,* 1986), discovered phi29 motor pRNA (*Science,* 1987), discovered pRNA hexamer (*Mol Cell,* 1998), pioneered RNA nanotechnology (*Mol Cell,* 1998*, Nature Nanotech,*2010), built a dual single molecule imaging system (*EMBOJ*, 2007), incorporated motor channel into lipid membrane (*Nature Nanotech, 2009*) for single molecule sensing. Currently, he is leading the emerging field of RNA nanotech for specific delivery of siRNA and drugs to cancers and viral infected cells. He received Pfizer Distinguished Faculty Award in 1995; Lions Club Cancer Res Award in 2006; Distinguished Alumni of the University of Minnesota in 2009, and Distinguished Research Award in 2010 and 2011, editor of five nanotech journals. His work has been reported hundreds of times over the radio or TV. and featured by NIH, NSF, MSNBC, NCI and ScienceNow, He was a member of two prominent national nanotech initiatives sponsored by NIST, NIH, and NSF; panelist of DOD medical assessment workshop; member of the review panel (site-visit) of National Cancer Institute Intramural Research Program, and member of NCI Alliance Coordination and Governance Committee, a $137M program of Nanotech in Cancer.

Fabrication of Thermodynamically and Structurally Stable RNA Nanoparticles for Specific Delivery of SiRNA and Drugs to Cancer and Viral Infected Cells.

Peixuan Guo[1], *Yi Shu*[1] *AND Qi-Xiang Li*[2]

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RNA can be manipulated with the simplicity of DNA, while mimics the versatile structure and catalytic function of proteins. Thermal stability made two nucleotides sufficient for annealing to produce multivalent nanostructures with defined stoichiometry for biotechnology and synthetic biology. With special properties in noncanonical base-pairing and base-stacking, RNA was designed to fold into well-defined structures and assembled into dimers, trimers, tetramers, and hexamers to harbor specialized functionalities via the interlocking left and right-hand loops. These nanoparticles were resistant to RNase digestion, did not dissociate after systemic injection, stable for drug and chemical conjugation, and demonstrated favorable pharmacokinetic properties *in vivo*. Controlling the ratio of 2'-modified ribonucleotides enabled the regulation of the stability for the desired *in vivo* circulation time frame. Building blocks of phi29 motor pRNA were constructed by a bipartite approach using two small, chemically-synthesized RNA fragments. The resulting RNAs nanoparticles harboring siRNA, drugs, aptamer and other functionalities were able to bind cancer cells specifically, enter the cell, and silence specific cancer genes. Chemically-modified, stable pRNA nanoparticles were readily manufactured through this scalable bottom-up assembly strategy, featuring total chemical synthesis and permitting diverse functional modularizations. The pRNA nanoparticles demonstrated a favorable PK profile in mice with a half-life ($T_{1/2}$) of 5~10 hr, significantly longer than the half life of conventional 2'-F modified siRNAs (0.25 hr). Repeated intravenous administrations in mice up to 30mg/kg did not result in a toxic effect, and did not induce an interferon response nor did it induce cytokine production. Fluorescent folate-pRNA nanoparticles dose-dependently targeted to FR^+ xenograft tumor in mice with minimal accumulation in normal tissues. This first comprehensive pharmacological study suggests that the pRNA nanoparticles possess all the preferred pharmacological features to serve as an efficient nanodelivery platform for broad medical applications.

Ref: Guo P, The Emerging Field of RNA Nanotechnology, **Nature Nanotechnology**, 2010 5:833

Wladek Minor

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EDUCATION:

1970 -1977 Ph.D. Solid State Physics, University of Warsaw, Poland
1964 -1969 M.Sc. Physics, University of Warsaw, Poland

EMPLOYMENT:

2003 - Professor, Dept. Molecular Physiology and Biological Physics, University of Virginia
1995- 2003 Associate Professor, tenured since 1998, Dept. Molecular, Physiology and Biological Physics, University of Virginia
1992 - 1995 Research Scientist, Biology Department, Purdue University
1989 - 1992 Assistant Research Scientist, Biology Department, Purdue University
1988 - 1989 Research Associate, Department of Biological Sciences, Purdue University
1985 - 1988 Postdoctoral Research Associate, Department of Physics, Purdue University
1985 Visiting Scientist, Royal Institute of Technology, Stockholm, Sweden
1979 - 1985 Adjunct, Department of Physics, University of Warsaw, Poland
1978 - 1979 Lecturer, Department of Physics, University of Warsaw, Poland
1969 - 1978 Research and Teaching Assistant, Department of Physics, U. of Warsaw, Poland

HONORARY APPOINTMENTS:

2009 - Visiting Professor, University of Liverpool, Liverpool, UK
2008 - Visiting Professor, Central South University, Changsha, China

AWARDS:

2007 Edlich-Henderson Inventor of the Year Award Curriculum Vitae Wladek Minor
1985 ASEA (Sweden) award for research on micro-crystallization of metallic glasses
1969 Award of the Polish Physical Society for M. Sc. Thesis

COMMITTEES AND ADVISORY BOARDS:

2007 - Executive Committee: Center for Structural Genomics of Infectious Disease
2000 - Executive Committee of the NIH Midwest Center for Structural Genomics
2004 - Executive Committee of the Faculty Forum for Scientific Research, University of Virginia
2006 - Journals of Structural and Functional Genomics - Editorial Board
2006 - NOBUGS Meeting
2007 European Materials Research Society Meeting

Research Publications: Over 110 papers with high impact.

Non-protein Components of Protein Structures and Other Biomedical Aspects of Structural Genomics and Drug Discovery

W. Minor, M. Chruszcz, H. Zheng, K. Majorek, P. Porebski

University of Virginia, Charlottesville, VA, 22908-0736, USAMidwest Center for Structural Genomics Center for Structural Genomics of Infectious Diseases New York Structural Genomics Consortium Enzyme Function Initiative

The three-dimensional structures determined by X-ray crystallography play a central role in understanding protein-small molecule and protein-protein interactions at the molecular level. Accurate details of such interactions have direct implications for drug design and development of other biomedical treatments. 3-D models have long been used to search for new drug targets, but only a fraction of new drugs coming to the market has been developed with the use of structure-based drug discovery. One reason for this disparity is that while over 90% of X-ray protein structures deposited in the Protein Data Bank contain ordered small molecules, including enzyme substrates and cofactors, the structural and chemical quality of small molecule models in protein structures does not correlate with overall structure quality. In particular, analysis of metal-protein interaction distances, coordination numbers, *B*-factors (displacement parameters), and occupancies of metal binding sites in protein structures determined by X-ray crystallography in the PDB shows many unusual values and unexpected correlations. Our work shows that small molecule models within PDB protein structures are usually not validated and thus require new approaches to the validation process.

In recent years there has been an explosion of new technologies for determining and analyzing structures now making their way into structure-based drug discovery. These developments, which result from Structural Genomics (SG) programs, will most likely improve our understanding of the molecular foundation of human diseases. SG programs have developed new methodology at all steps of the structure determination process, not only to determine new structures in a highly efficient way, but also to study protein-ligand and protein-protein interactions. I will present some of these tools, and describe an example of their use: the structure determination and analysis of structures of dust mite allergens, and their complexes with antibody fragments. This analysis provides insight into the mechanisms of allergenicity and cross-reactivity of these allergens. Finally, we will discuss the conditions that must be met to convert the present high-throughput structure determination pipeline into a high-output structure-based drug discovery system.

Rongqiao He (赫荣乔)

Dr Rongqiao He graduated from Luzhou Medical College in Sichuan province in 1982; defended for M.S. in Dept of Cytology of Institute of Microbiology, Chinese Academy of Sciences (CAS) in 1989, and obtained Ph. D (Enzymology) in National laboratory of Biomacromolecules in Institute of Biophysics CAS. Now, he works in the State Key Laboratory of Brain and Cognitive Science, Institute of Biophysics (CAS). The major interest is protein science and neurodegeneration. He has ever visited and cooperatively worked with the colleagues in Dept of Biochemistry University of Cambridge, UK; Collagen Research group Division of Molecular and cellular biology, Bristol University, UK; Dept of Pharmacy, University of Nottingham, UK; Lady Davis institute for Medical Research, McGill University, Canada; Dept of Biophysics and Biochemistry, Pisa University, Italy; and Dept Neurochemistry, the State Institute of Basic Research of Disabilities, New York, USA. So far, his group works in protein misfolding, aggregation and neurodegeneraiton.

Endogenous formaldehyde as one of risk factors involving sporadic Alzheimer's disease.

Rong Qiao He

State Key Laboratory of Brain and Cognitive Sciences, Institute of Biophysics; Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, Beijing 100101, China

Formaldehyde is one of the most toxic organic compounds, which is produced and processed by human cells at each moment. As shown in our results, the level of human endogenous formaldehyde is kept at low concentration (0.01-0.08 mM) in urine under physiological condition, but the concentration is getting higher during aging. The endogenous formaldehyde level higher than the physiological concentration induces misfolding of neuronal protein for instance Tau protein resulting in cytotoxic products. The formaldehyde-treated Tau protein existed in globule-like aggregations. Abnormal high level of formaldehyde leads to dysfunction of the central nerve system including dysfunction in cognition. Furthermore, GSK-3β was up-regulated in the presence of formaldehyde added to the culture of SY5Y cells by using Illumina Solexa DNA sequencing and western blotting. This suggests that abnormal formaldehyde concentrations is related to hyper-phosphorylation. The urine formaldehyde concentrations were significantly different between Alzheimer's disease elders' (n=30) and normal elders' (n=30) ($t=8.572$, $P<0.001$). The level of urine formaldehyde is recommended as a candidate biomarker to support clinical diagnosis.

Xiao-Dong Su (苏晓东)

Dr. Xiao-Dong Su has obtained his B.Sc. in solid state physics 1985, at Department of Physics, Peking University, China; and did Graduate study at the Dept. of Biophysics, Beijing Medical College, Peking University during 1985-1987; 1988-1994, he was Ph.D. candidate at the Department of Cell and Molecular Biology, Karolinska Institute, Sweden; 1995-1998, Research associate with Howard Hughes Medical Institute (HHMI) at Division of Biology, California Institute of Technology, USA; during 1998-2001, he was assistant professor at the Department of Molecular Biophysics, Chemistry Center, Lund University, Sweden; and during 2001-2002, associate Professor at Department of Molecular Biophysics, Chemistry Center, Lund University, Sweden; From 2003 to present, he is professor at the Department of Biochemistry and Molecular Biology, College of Life Sciences, Peking University. His current positions include Secretary-general of Chinese crystallography Society (CCrS); Deputy Director of Biodynamics Optical Imaging Center (BIOPIC), Peking University, China, and Associate Director, National Lab. of Protein Engineering & Plant Genetic Engineering;

Research Interests:

The Su lab is interested in structural and functional studies of proteins/genes related to human diseases or with important functions. The Su lab has built up technological platforms for high-throughput (HTP) methods for structural genomics (structural biology) studies, including target selection; HTP and automated gene cloning; protein expression; protein purification; crystallization and crystal structure determinations. The lab has also developed the Single-wavelength Anomalous Diffraction methods on the copper rotating anode (in-house S-SAD). In addition to *E. coli* expression systems, eukaryotic systems such as baculovirus system have been tried as well to express proteins that are hard to do in prokaryotic expression systems.

Caspase-6 as drug target for neurodegenerative diseases

Xiao-Dong Su

Department of Biochemistry and Molecular Biology, College of Life Sciences, Peking University

Caspases represent a family of cysteine proteases involved in apoptosis and inflammation. The short pro-domain effector (also called executioner) caspase-6 (Casp6) is strongly associated with neurodegeneration and axonal pruning, and plays an important role in Alzheimer disease and Huntington disease. Our structural and biochemical results on a few different types of Casp6 (zymogen, inhibitor bound Casp6 and pseudo-phosphorylated Casp6) revealed novel intramolecular self-cleavage mechanism for Casp6 activation, disclose the inhibition mechanism of phosphorylation at Ser257, and draw a whole picture of Casp6 self-activation and regulation. These different structures of Casp6 provide structural basis for designing specific inhibitors of Casp6 and developing efficient therapeutic treatment against neurodegenerative diseases, such as Alzheimer disease and Huntington disease.

Wayne Foster Anderson

Education:

1970 B.Sc. (Summa Cum Laude) Biochemistry University of Minnesota

1975 Ph.D. Molec. Biophys. & Biochem Yale University

Professional Experience:

1975-77 Research Associate, Institute of Molecular Biology University of Oregon, Eugene, Oregon

1977-79 NIH Postdoctoral Fellow, Institute of Molecular Biology U. Oregon, Eugene, Oregon

1979-88 Assistant and Associate Professor, Department of Biochemistry Member, MRC Group in Protein Structure and Function, University of Alberta, Edmonton, Alberta

1988-94 Professor, Department of Biochemistry, Vanderbilt University, Nashville, TN

1994- Professor, Department of Molecular Pharmacology & Biological Chemistry Northwestern U

2000- Member, Midwest Center for Structural Genomics

2002- Scientific Director, Advanced Photon Source Life Sciences Collaborative Access Team (LS-CAT)

2005- Co-Director, Northwestern University Synchrotron Research Center

2007- Director, Center for Structural Genomics of Infectious Diseases

Selected Publications: (Over 325 Protein Databank (PDB) Deposits and 100 publications)

1. Anderson, W.F., D.H. Ohlendorf, Y. Takeda and B.W. Matthews. Structure of the Cro repressor from bacteriophage □ and its interaction with DNA. Nature **290**: 754-758 (1981).
2. Rajan, S.S., X. Yang, F. Collart, V.L.Y. Yip, S.G. Withers, A. Varrot, J. Thompson, G.J. Davies and W.F. Anderson. Novel catalytic mechanism of glycoside hydrolysis based on the structure of an NAD+/Mn2+-dependent phospho-□ -glucosidase from Bacillus subtilis. Structure **12**:1619-1629 (2004).
3. Yip, V.L.Y., A. Varrot, G.J. Davies, S.S. Rajan, X. Yang, J. Thompson, W.F. Anderson and S.G. Withers. An unusual mechanism of glycoside hydrolysis involving redox and elimination steps by a family 4□ -glycosidase from *Thermotoga maritima*. Journal of the American Chemical Society **126**:8354-8355 (2004).
4. Rajan, S.S., X. Yang, L. Shuvalova, F. Collart and W.F. Anderson. Crystal structure of YfiR, an unusual TetR/CamR-type putative transcriptional regulator from Bacillus subtilis. Proteins: Structure, Function and Bioinformatics **65**:255-257 (2006).
5. Vorontsov, I.I., G. Minasov, J.S. Brunzelle, L. Shuvalova, O. Kirykhina, F.R. Collart and W.F. Anderson. Crystal structure of an apo form of *Shigella flexneri* ArsH protein with an NADPH-dependent FMN reductase activity. Protein Science **16**:2483-2490 (2007). PMCID: PMC2211697.
6. Filippova, E.V., J.S. Brunzelle, M.E. Cuff, H. Li, A. Joachimiak and W.F. Anderson. Crystal Structure of the Novel PaiB Transcriptional Regulator from *Geobacillus stearothermophilus* Involved in the Negative Control of Sporulation and Degradative Enzyme Production. Proteins: Structure, Function and Bioinformatics accepted for publication (2011).
7. Minasov, G., S. Padavattan, L. Shuvalova, J.S. Brunzelle, D.J. Miller, A. Baslé, C. Massa, F.R. Collart, T. Schirmer, and W.F. Anderson. Crystal structures of YkuI and its complex with second messenger cyclic-di-GMP suggests catalytic mechanism of phosphodiester bond cleavage by EAL domains. Journal of Biological Chemistry **284**:13174-13184 (2009). PMCID: PMC2676049.

Insights from Structural Genomics projects focused on infectious diseases

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Center for Structural Genomics of Infectious Diseases and [1]Northwestern University, Chicago, IL, [2]University of Toronto, Toronto, ON, [3]Washington University, St Louis, MO, [4]University of Chicago, Chicago, IL, [5]University of Virginia, Charlottesville, VA, [6]University College London, London, GB, [7]University of Texas Southwestern Medical Center, Dallas, TX, and [8]JC Venter Institute, Rockville, MD

Structural genomics approaches and high throughput structure determination applied to proteins from organisms that cause infectious diseases provides the three-dimensional structures for many proteins that are potential drug targets. The resulting array of structures is a starting point for structure aided drug discovery efforts. The Center for Structural Genomics of Infectious Diseases (CSGID) is applying state-of-the-art structural biology technologies to the characterization of proteins from the National Institute for Allergy and Infectious Diseases (NIAID) category A-C pathogens and organisms causing emerging, or re-emerging infectious diseases. CSGID target selection emphasizes potential biomedical relevance. Selected proteins include known drug targets and their homologs, essential enzymes, virulence factors and vaccine candidates. Suggestions for target proteins are solicited from the broader scientific community and 25% of CSGID target proteins arise from community requests. The CSGID is also interested in establishing collaborations whose aim is to combine the structural results with follow-up functional studies. The ultimate goal is to generate a library of structures for proteins and their complexes with small molecules that are available to the scientific community and can contribute to further research and structure aided drug discovery for infectious diseases. The CSGID has already deposited over 300 structures from bacterial pathogens into the Protein Data Bank. Additionally, expression clones for over 1500 proteins are available through BEI Resources. These structures are providing important structural insights on metabolic pathways that are potential drug targets and on proteins that are potential sites of interaction with the host, such as surface exposed proteins.

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Keqiong Ye (叶克穷)

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Education

B.S. Department of Biological Science and Technology, Zhejiang University 1995

Ph.D. Institute of Biophysics, Chinese Academy of Sciences (Dr. Jinfeng Wang) 2000

Professional Positions

Associate Investigator, National Institute of Biological Sciences, Beijing 2011-present

Assistant Investigator, National Institute of Biological Sciences, Beijing 2005-2011

Research fellow, Research Associate, Senior Research Scientist, Memorial Sloan Kettering Cancer Center, New York, USA. (with Dr. Dinshaw J. Patel) 2001-2005

Research Interest

Numerous non-coding RNAs function as structural, catalytic and regulatory molecules and they frequently work by forming RNA-protein complexes. We are interested in RNA-protein interactions occurring in RNA silencing, RNA-guided RNA modification enzymes and eukaryotic ribosome biogenesis. Our main approaches are X-ray crystallography, NMR and biochemical analysis.

Honors and Awards

First Honor Di-Ao Fellowship, Chinese Academy of Sciences 2000

Membership in Professional Societies:

Chinese Biophysical Society, Committee Member of Molecular Biophysics since 2009

Chinese Crystallographic Society

Representative publication:

1. Lin J., Lai S., Jia R., Xu A., Zhang L.,Lu J. and Ye K. 2011 Structural basis of site-specific ribose methylation by box C/D RNA protein complexes. *Nature* 469: 559-563.
2. Ye K., Jia R., Lin J., Ju M., Peng J., Xu A. and Zhang L. 2009 Structural organization of box C/D RNA-guided RNA methyltransferase. *Proc Natl Acad Sci USA*, 106: 13808-13813.
3. Duan J., Li L., Lu J., Wang W. and Ye K. 2009. Structural mechanism of substrate RNA recruitment in H/ACA RNA-guided pseudouridine synthase. *Mol Cell* 34:427-439.
4. Li, L. and Ye, K. 2006. Crystal structure of an H/ACA box ribonucleoprotein particle. *Nature* 443: 302-307. Article
5. *Ma, J., *Ye, K. and Patel, D.J. 2004. Structural mechanism of overhang-specific small interfering RNA recognition of the PAZ domain. *Nature* 429:318-322. (*equal contribution)
6. Ye, K., Malinina, L. and Patel, D.J. 2003. Recognition of small interfering RNA by a viral suppressor of RNA silencing. *Nature* 426:874-878.

Unusual binding of DNA repeats by a plasmid partition protein ParB

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Stable transmission of duplicated genetic material to daughter cells is essential for all life forms. The active partitioning system of low-copy-number plasmids is a simple model for DNA segregation study and is composed of only three elements: a centromere region composed of DNA repeats, a centromere-binding protein ParB and a filament-forming NTPase ParA. During plasmid partition, multiple ParB proteins assemble on the centromere repeats to form a higher-order nucleoprotein complex, the partition complex, which in turn recruits ParA. ParA can polymerize into filaments in an NTP dependent manner and separate the attached plasmids into the opposite poles of dividing cells. We have studied a type Ib partition complex from plasmid pCXC100 through biochemical and structural approaches. We showed that the C-terminal DNA-binding domain of ParB adopts a dimeric ribbon-helix-helix (RHH) fold. The centromere core comprises nine uninterrupted 9-nucleotide direct repeats that can be successively bound by ParB dimers in a cooperative manner. Interestingly, the interaction of ParB with a single subsite requires 18 base pairs covering one immediate repeat as well as two halves of flanking repeats. Mutagenesis analysis further revealed that the repeat sequence is jointly specified by adjacent ParB dimers bound to an overlapped region. We have now solved the crystal structure of ParB bound to tandem DNA repeats, providing a model to explain the unusual centromere recognition mechanism.

Floyd Eric Romesberg

Education

1994 Ph.D. in Organic Chemistry, Cornell University, Ithaca, NY.

1990 M.S. in Organic Chemistry, Cornell University, Ithaca, NY.

1988 B. S. in Chemistry, Ohio State University, Columbus, OH

Academic and Research Experience

2006-present Associate Professor, Department of Chemistry, The Scripps Research Institute

1998-2006 Assistant Professor, Department of Chemistry, The Scripps Research Institute

1994-1998 NIH Postdoctoral research fellow under Peter G. Schultz, Department of Chemistry, UC Berkeley, Berkeley, CA

1988-1994 Ph.D. candidate under David B. Collum, Department of Chemistry, Cornell University, Ithaca, NY

1986-1988 Undergraduate research student under Matt Platz, Department of Chemistry, The Ohio State University, Columbus, OH

Selected Publications (from over 120 publications)

1. 1.A. M. Leconte, M. P. Patel, L. E. Sass, P. McInerney, M. Jarosz, L. Kung, J. L. Bowers, P. R. Buzby, J. W. Efcavitch, F. E. Romesberg (2010) Directed evolution of DNA polymerases for next-generation sequencing. Angew. Chem. Int. Ed. Engl. 49:5921-5924.
2. P. Weinkam, J. Zimmermann, F. E. Romesberg, P. G. Wolynes (2010) The folding energy landscape and free energy excitations of cytochrome *c*. *Acc. Chem. Res.* 43:652-660.
3. D. Malyshev, Y. J. Seo, P. Ordoukhanian, **F. E. Romesberg**. (2009) PCR with an expanded genetic alphabet. *J. Am. Chem. Soc*., 131:14620-14621.
4. Y. J. Seo, **F. E. Romesberg**. (2009) Major groove derivatization of an unnatural base pair. *ChemBioChem*, 10:2394-2400 [cover story]
5. G. T. Hwang, Y. Hari, **F. E. Romesberg**. (2009) The effects of unnatural base pairs and mispairs on DNA duplex stability and salvation. *Nucleic Acids Res.*, published online 10 June 2009
6. M. E. Cremeens, J. Zimmermann, W. Yu, P. E. Dawson, **F. E. Romesberg**. (2009) Direct observation of structural heterogeneity in a β-sheet. *J. Am. Chem. Soc.* 131:5726-5727
7. M. T. Thielges, J. Zimmermann, **F. E. Romesberg.** (2009) Direct observation of ligand dynamics in cytochrome *c J. Am. Chem. Soc.* 131:6054-6055
8. Y. J. Seo, S. Matsuda, **F. E. Romesberg**. (2009) Transcription of an expanded genetic alphabet. *J. Am. Chem. Soc.* 131:5046-5047
9. D. Groff, M. C. Thielges, S. Celliti, P. G. Schultz, **F. E. Romesberg**. (2009) Efforts toward the direct experimental characterization of enzyme microenvironments: tyrosine 100 in dihydrofolate reductase. *Angew. Chem., Int., Ed.,* 48:3478-3481
10. Y. J. Seo, G. T. Hwang, P. Ordoukhanian, **F. E. Romesberg**. (2009) Optimization of an unnatural base pair towards natural-like replication. *J. Am. Chem. Soc.,* 131:3246-3252
11. D. Groff, M. C. Thielges, S. Celliti, P. G. Schultz, **F. E. Romesberg**. (2009) Efforts toward the direct experimental characterization of enzyme microenvironments: tyrosine 100 in dihydrofolate reductase. *Angew. Chem., Int., Ed.,* 48:3478-3481

Expansion of the Genetic Alphabet

Floyd Eric Romesberg

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Expansion of the genetic alphabet to include a third base pair would be a fundamental accomplishment that would not only have immediate utility for a number of applications, such as site-specific oligonucleotide labeling, but would also lay the foundation for an organism with an expanded genetic code. Toward this goal, we have examined a large number of different unnatural nucleotides bearing mainly hydrophobic nucleobase analogs that pair based predominantly on packing and hydrophobic interactions rather than H-bonding. Extensive structure-activity relationship studies have resulted in the optimization of the unnatural base pairs for replication by DNA polymerases. In addition we have used two screens of more than 3600 possible unnatural base pairs to identify one that is efficiently replicated. Optimization of the initial lead resulted in the an two unnatural base pair, d**5SICS**-d**NaM** that is stable in duplex DNA, is efficiently synthesized by DNA polymerases, and is efficiently transcribed into RNA by an RNA polymerase. Derivatives with linkers attached are also efficiently incorporated site-specifically into DNA and RNA, allowing for their post-synthesis derivatization and site-specific labeling of DNA or RNA with virtually any functionality. Several applications, including ongoing unnatural DNAzyme selection will be discussed. Finally, we are supplementing these efforts with directed evolution to tailor DNA polymerases to more efficiently replicate DNA containing our unnatural bases. Our approach involves an activity-based phage display selection system, wherein libraries of polymerase mutants are displayed on phage along with their unnatural substrates. The desired polymerase activity results in the incorporation of a biotin-tagged nucleotide and allows for the selective isolation of active mutants. Using this system, we have identified polymerase variants with interesting unnatural activities, including the improved replication of DNA containing unnatural base pairs.

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1983 BSc Central China Normal University
1991 MSc Central China Normal University
1999 PhD Wuhan University
1983-1988 Lecturer, Xianning College
1991-1999 Associate Professor, Central China Normal University
2000-2001 Royal Society Research Fellow, University of Edinburgh
2002-2006 Research Associate, University of Edinburgh
2007- Professor, Institute of Chemistry, CAS

Research Interests:

1. Research and development of organometallic ruthenium anticancer agents
2. Molecular basis for the action of anticancer agents.
3. Mass spectrometry

Selected Publications:

1. The anticancer drug cisplatin can cross-link the interdomain zinc site on human albumin, Hu, W. B.; Luo, Q.; Wu, K.; Li, X. C.; Wang, F. Y.* Chen, Y.; Ma, X. Y.; Wang, J. P.; Liu, J. A.; Xiong, S. X.; Sadler P. J.*, ***Chem. Commun.*** 2011, *47,* 6006-6008
2. The formation of thymidine-based t-tetramers with remarkable structural and metal ion size effects,Luo, Q.; Wu, D. Y.; Liu, S. X.; Tang, D. H.;* Huang, Y.; Liu, X. H.; Wang, F. Y.;* Wang, R. Y.; Wu, G..;* ***Org. Biomol. Chem.,*** 2011, *9,*1030-1033
3. Arene control over thiolate to sulfinate oxidation in albumin by organometallic ruthenium anticancer complexes, Hu, W. B.; Luo, Ma, X. Y.; Wu, K.; Liu, J. A.; Chen, Y.; Xiong, S. X.; Wang, J. P.;* Sadler, P. J.;* Wang, F. Y.* *Chem. Eru. J.* **2009**, *15*, 6586-6594
4. Controlling ligand substitution reactions of organometallic complexes: tuning cancer cell cytotoxicity, Wang, F. Y.; Habtemariam, A.; van der Geer, E. P. L.; Fernández, R.; Melchart, M.; Deeth, R. J.; Aird, R.; Guichard, S.; Fabbiani, F. P. A.; Lozano-Casal, P.; Oswald, I. D. H.; Jodrell, D. I.; Parsons, S.; Sadler, P. J.* *Proc. Natl. Acad. Sci. U. S. A.* **2005**, *102*, 18269-18274
5. Competition between glutathione and guanine for a ruthenium(II) arene anticancer complex: detection of a sulfenato intermediate, Wang, F. Y.; Xu, J.; Habtemariam, A.; Bella, J.; Sadler, P. J.* *J. Am. Chem. Soc*. **2005**, *127*, 17734-17743

Interactions of Metal-based Anticancer Agents with Serum Albumin

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Intravenously-injected metallodrugs are readily to interact with serum proteins, in particular albumin. Such interactions may have a crucial effect on the bioavailability and transport and metabolism of metallodrugs. Therefore, there is a great need for further advances in understanding the metal coordination chemistry of serum albumin. In the present work, we have comparatively studied the interactions of two organometallic ruthenium anticancer complexes [η^6-arene)Ru(en)Cl]PF_6, (arene = *p*-cymene (**1**) or biphenyl (**2**)) and cisplatin with human serum albumin (HSA), and identified sequence-specific binding sites using mass spectrometry. We found that both of complexes **1** and **2** bind to surface histidines (His128, His247, His510) and methionine (Met298) in recombinant human albumin (rHA), but only the *p*-cymene complex can gain entry to the crevice containing the free cysteine thiolate (Cys34) and induce oxidation to sulfinate. The surface residues Met298, His128 and His247 are also the main binding sites of cisplatin to rHA. And cisplatin was also found to induce the cleavage of the disulfide bond Cys124-Cys169 followed by cisplatin coordination to Cys124. Interestingly, for the first time cisplatin is shown to crosslink residues His67 of domain I and His247 of domain II in rHA, occupying the major binding site for transport of zinc, providing a possible link between the clinic use of cisplatin and hyperzincuria and hypozincemia observed in patients.

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Keywords:

Anticancer Metallodrugs / Albumin / Interaction / Binding Site / Mass Spectrometry

Li Niu

Dr. Li Niu is currently an Associate Professor in the Department of Chemistry, the Center of RNA Institute and the Center for Neuroscience Research, at the State University of New York (SUNY) at Albany. He received his Ph.D. in chemistry/biochemistry from the University of Wisconsin, Milwaukee studying flavoproteins. He pursued his first postdoctoral training at Cornell University with Professor George P. Hess where he worked on ion channel proteins. In late 1997, he joined Professor Gobind Khorana's research group at Massachusetts Institute of Technology where he studied rhodopsin, a GPCR, in visual signal transduction pathway. Dr. Niu joined the faculty at SUNY-Albany in 2000. His group is investigating the structure-function relationship and the mechanism of regulation of glutamate ion channel receptors. His group is also developing RNA aptamers as a new class of glutamate receptor regulating molecules.

Selected Publications

1. Park, J.S., Wang, C.Z., Han, Y., Huang, Z. & Niu, L. (2011) *J. Biol. Chem.* **286**,15608-15617. Epub 2010 March 14, 2011. Potent and selective inhibition of a single AMPA receptor subunit by an RNA aptamer.
2. Han, Y., Wang, C.Z., Park, J.S. & Niu, L. (2010) *Biochemistry* **49**, 9207-9216 Epub 2010 October 8. Channel-Opening Kinetic Mechanism for a Human Wild-Type GluK2 and a C-terminal Mutant Kainate Receptor
3. Huang, Z., Han, Y., Wang, C.Z., & Niu, L. (2010) *Biochemistry* **49**, 5790-5798. Epub 2010 June 21. Potent and Selective Inhibition of the Open-Channel Conformation of AMPA Receptors by an RNA Aptamer
4. Huang, Z., Pei, W.M., Han, Y., Jayaseelan, S., Shekhtman, A., Shi, H. & Niu, L. (2009) *Nucleic Acids Research* **37**, 4022-4032. Epub 2009 May 5. One RNA aptamer sequence, two structures: a collaborating pair that inhibits AMPA receptors.
5. Pei, W.M., Huang, Z., Wang, C.Z., Han, Y., Park, J.S. & Niu, L. (2009) *Biochemistry* **48**, 3767-3777. Epub 2009 March 10. Flip and Flop: a Molecular Determinant for AMPA Receptor Channel Opening (this article has been chosen to be highlighted on the journal's home page for this issue)
6. Ritz, M., Micale, N., Li, G., Grasso, S. & Niu, L. (2008) *Biochemistry* **47**, 1061-1069. Epub 2007 Dec 28. A Laser-Pulse Photolysis Study of the Mechanism of Inhibition of the GluR2 AMPA Receptor by 2,3-Benzodiazepine Derivatives
7. Pei, W.M., Ritz, M., McCarthy, M., Huang, Z. & Niu, L. (2007) *J Biol Chem*. **282**, 22731-22736. Epub 2007 Jun 1. Receptor occupancy and channel-opening kinetics: a study of GluR1 L497Y AMPA receptor
8. Huang, Z., Pei, W.M., Shi, H. & Niu, L. (2007) *Biochemistry* **46**, 12648-12655. Epub 2007 Oct 12. RNA aptamers selected against the GluR2 AMPA receptor expressed in HEK-293 cells

Developing RNA Aptamers as Drug Candidates Targeting Glutamate Ion Channels

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In finding a new treatment for a number of neurological disorders and diseases, such as epilepsy, stroke and amyotrophic lateral sclerosis (ALS), one of the potential therapeutic strategies is to develop inhibitors for the α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors, a receptor subtype in the glutamate ion channel receptor family. This is because excessive activity of AMPA receptors leads to abnormal calcium influx into neurons, which in turn leads to cell death. In developing AMPA receptor inhibitors that are both potent and water soluble, we have used systematic evolution of ligands by exponential enrichment (SELEX) and have successfully identified three classes of aptamers with nanomolar affinity against AMPA receptors. In the class of competitive aptamers, we found one aptamer with an IC50 value of 30 nM, rivaling any other exiting AMPA receptor inhibitors. Furthermore, this aptamer is broadly active in all AMPA receptor subunits, but has no unwanted activity in either kainate or NMDA receptors, the two other glutamate receptor subtypes. We have also identified two other classes of noncompetitive aptamers that are selective to different conformations of GluR2, a key AMPA receptor subunit that mediates glutamate-induced cell toxicity. One class uniquely inhibits the open-channel conformation whereas the other inhibits the closed-channel conformation of GluR2. The latter in fact is single-subunit selective aptamer designed to target GluR2 only. To turn these aptamers into potentially useful drugs, we have now successfully developed a class of chemically modified aptamers that are highly resistant to ribonucleases so that these aptamers can be tested *in vivo*. Our results demonstrate the possibility of developing RNA aptamers against AMPA receptor channels with nanomolar affinity, excellent water solubility and superior selectivity to AMPA receptors and even to a single AMPA receptor subunit. These aptamers are therefore potential templates for design of better inhibitors as new drug candidates for a number of neurological disorders and diseases.

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Research Theme Application of NMR spectroscopy to characterise the structure, dynamics and interactions of nucleic acids (DNA,RNA) , proteins and their complexes.

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Research Grants BBSRC, EPSRC, MRC, Wellcome Trust, AICR, Nuffield Foundation, BSAC, MRC National Biomedical NMR Facility, N.I.M.R., Mill Hill, London and Large scale EU BIO-NMR Facility, France.

Recent invited talks EU Bio-NMR Annual Meeting, Brno, Czech Republic, 24-27 Jan 2011
17th Annual NMR Society (India) Meeting, held in honour of Nobel Laureate Richard Ernst and Prof Alex Pines, Amritsar, India, 1-4 April 2011.

Teaching Portfolio NMR spectroscopy; Biophysical Chemistry; NMR in Cheminformatics; Chemistry for Life Scientists

Selected Publications

1. Narukulla R, Shuker DE, Ramesh V, Xu YZ. Unambiguous structural elucidation of base-modified purine nucleosides using NMR. **Magnetic Resonance in Chemistry**. **2008** January; 46: 1-8.
2. Shammas, Christos; Donarski, James and Ramesh, Vasudevan. NMR structure of the *peptidyl transferase* inhibitor antibiotic amicetin. **Magnetic Resonance in Chemistry. 2007;** 45: 133-141.
3. Donarski, James ; Shammas, Christos; Banks, Ryan and Ramesh, Vasudevan. NMR and Molecular Modelling Studies of the Binding of Amicetin Antibiotic to Conserved Secondary Structural Motifs of 23S Ribosomal RNAs. **The Journal of Antibiotics**. **2006;** 59: 177-183.
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1 GHz NMR investigation of the binding of *peptidyl transferase* inhibitor antibiotics to conserved secondary structural motifs of 23S ribosomal RNAs.

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The growing challenge of antibiotic resistance being witnessed in recent times has prompted intense efforts to elucidate the mechanism of action of antibiotics at the molecular level. Blocking protein synthesis is an effective way of combating bacterial infection and many antibiotics function in just this manner. The most important functional site on the ribosome is the *'peptidyl transferase centre'* and previous resistance studies using a number of antibiotics have located this within 23S like rRNAs in the highly conserved central circle of domain V. We have successfully determined the NMR structures of the RNA binding, peptidyl tranferase inhibitor antibiotics Amicetin, Blasticidin S and Gougerotin and the structures all exhibit a stable conformation, stabilised by intramolecular hydrogen bonds.[1] Amicetin was observed to be folded, distinctly different from the linear, extended conformation previously determined by X-ray crystallography.[2] All the NMR structures revealed a similar conformation in the analogous regions of their chemical structure, suggesting that hybrid antibiotics could be generated.

The NMR structures of the amicetin binding *E. coli.* 29-mer, *H. h.* 29- and 37-mers and *B. subtilis* 27-mer RNA motifs have been determined using ultra high field 1 GHz spectroscopy and all the motifs form stable, well folded A-form RNA conformations.[1] Addition of Amicetin to the RNA samples were accompanied by discrete changes to the spectra which can be interpreted to changes induced in the local conformation of the RNA motifs and the Amicetin, arising from the formation of a complex, between the Amicetin and the bulge region of the particular motif.[1,3]

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3. J. Donarski, C. Shammas, R. Banks and V. Ramesh (2006) ***J. Antibiotics***, 59(3) 177-183

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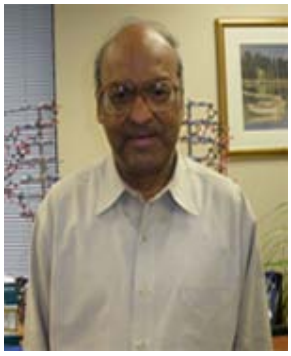
Suresh C. Srivastava



Dr. Suresh C. Srivastava is founder & president of ChemGenes Corp. USA. Dr. Srivastava received his Ph.D. in organic chemistry from Lucknow University, India in 1968. Dr. Srivastava continued research in synthetic organic chemistry for additional two years at Central Drug Research Institute, Lucknow India. He moved to United States in year 1970 and joined Roswell Park Memorial Institute, Buffalo, New York and carried out research and development in anticancer therapeutics research. Susequently in year 1972, Dr. Srivastava moved to Research Triangle Institute, Raleigh < north Carolina, USA as scientist and carried out synthetic efforts in total synthesis of a terpenoid molecule called a Strigol. After one year Dr. Srivastava took research scientist position at Purdue University, Lafayette, Indiana , USA and stayed there till year 1976. At Purdue University, deparment of Chemistry as well as department of medicinal chemistry, Dr, Srivastava carried out research in antibiotics, Mitomycin; synthetic and mechanistic aspect in organo palladium chemistry. Subsequently Dr. Srivastava moved to Boston Biomedical Research Institute as Staff Scientist and stayed there till year 1981. There he carried out extensive chemistry of nucleosides and synthesized a number of oligonucleotides, utilizing phosphodiester and phosphotriester methodologies.

In the year 1981, Dr. Srivastava started ChemGenes Corporation, a biotechnology company. The company has been in operation since then. Currently located in Wilmington, Massachusetts, has been a strong partner to researchers engaged in the field of DNA/RNA synthesis for almost 30 years. **ChemGenes**, the industry leader in Oligonucleotide Reagent manufacturing, high quality phosphoramidites and solid Supports in the market. ChemGenes faciltyis setup for therapeutic grade phosphoramidites and DNA/RNA synthesis products suitable for GMP grade oligonucleotide manufacturing. ChemGenes' product lines include phosphoramidites for DNA and RNA synthesis, antisense phosphoramidites, modified bases for DNA and RNA modification. In addition, we produce a variety of modified phosphoramidites for the introduction of chromophores and ligands. The availability of high quality solid supports, prepacked disposable columns of various pore sizes, loadings, low volume columns, ancillary reagents in configurations suitable for each synthesizer, and DNA purification cartridges.

Current ChemGenes Patents & Licenses:

ChemGenes 2' O-Methyl p-ethoxy patent #6,015,886
ChemGenes 2'-O-Methyl patent, patent #5,525,719,
ChemGenes 3'-O-Methyl patent #5,525,719
ChemGenes 2'-propargyl modified patent #5,744,595
ChemGenes 3'-propargyl modified Amidites & Solid Supports patent#5,744,595
Qiagen Inc. TOM Amidites Patent #5,986,084

*UNYLINKERTM is a Trademark of Isis Pharmaceuticals, Inc. The above products are covered under Isis patent #7,202,264. and ChemGenes Corp. holds world wide marketing rights.

MODERN TECHNOLOGIES FOR HIGH PURITY RNA SYNTHESIS

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This invention developed at ChemGenes Corp. relates to novel process of RNA synthesis in reverse 5' → 3' direction. The approach leads to very clean oligonucleotide synthesis allowing for synthesis of high purity and therapeutic grade RNA oligonucleotides and introduction of various modifications at the 3'- end cleanly. Detailed comparative data analysis was carried out after synthesis and purification of RNA's by both conventional method (3'→5') and reverse direction (5'→3'). We observed consistent high purity of RNAs synthesized by reverse Direction (5'→3'). Furthermore smooth 3'- Conjugation of various macromolecules such as cholesterol, HEG and PEG (Polyethylene glycols) occurs in high yield resulting in high purity oligonucleotides. Using this method we demonstrated high quality RNA synthesis with coupling efficiency surpassing above 99% per step. We observed almost complete absence of N+1 in Reverse RNA Synthesis consistently even when the last amidite was a macromolecule and this resulted in very high purity of HPLC purified and 3'-modified oligonucleotides. The method is getting very popular & useful for RNA synthesis in general, high throughput RNA synthesis and especially for RNA oligonucleotides which require 3'- modifications. The phosphoramidites, A-n-bz, C-n-bz, C-n-ac, G-n-ac and U are produced with an HPLC purity of greater than 98% and ^{31}P NMR purity greater than 99%.

2'- ALE- 5'- NPPOC-Nucleoside Phosphoramidites & application for High Density RNA Chip Micro Array: A brief detail of this technology will be presented.

Fabrication of RNA microarrays has severely lagged behind. The few reports available in the literature describe the immobilization of several pre-synthesized RNA strands directly on the chip. This is mainly due to lack of ideal RNA Synthesis monomer synthons which can carry photolabile group. With 2'- ALE-NPPOC amidites RNA microarray synthesis and design has been made possible. The applications include Genomic Selection; RNA Synthetic Biology; Gene expression profiling;Aptamer Optimization; Biomarker Validation; point-of-care handheld devices; RNA Biochips manufactured exactly to precise specifications & high-throughput and flexible technology for miRNA analysis and targeted re-sequencing, is planned by a number of Gene Chip synthesizer.

Pivom Protected RNA Synthons:

A highly useful technology which involves single step deprotection of RNA olgomers will be briefly described.

Ping Yang

Dr. Yang, Ping currently serves as global business leader at GENEWIZ and general manager of GENEWIZ China. His previous careers include general manager of GENEWIZ Beijing. Before joined GENEWIZ in 2009, Dr. Yang was Gene department director of GeneScript where he established and supervised one of the largest Gene synthesis facility in the world within 3 years. He led a team created an advanced gene synthesis platforms that turns out a time and cost effective replacement for traditional gene/DNA cloning. As his new role as global gene synthesis business leader, Dr. Yang brings more than 15 years of researching, technology and development expertise to GENEWIZ where he is responsible for building and leading the Company's next generation of genetic analysis, gene synthesis, a wide range of molecular biology services, antibody engineering services and GLP services. Before his career in CRO industry, Dr, Yang was a research faculty at Vanderbilt University where he was a co-investigator of 2 NIH sponsored grants focusing on the pharmacogenomics and personalized drug effects on the ion channels, and he served as scientist and senior scientist focusing on the pharmacology studies in drug development at Janssen Research Foundation in Belgium and Palatin Pharmaceuticals in New Jersey. Dr. Yang did his Ph.D. graduate research in molecular genetics and pharmacology. After obtained his Ph.D degree, Dr. Yang conducted his post-doctoral research on the pharmacogenomics and clinical pharmacology with Dr. Dan Roden at Vanderbilt University. Dr. Yang has authored and co-authored over 50 publications and he has been an invited speaker at many scientific symposiums.

De novo DNA Synthesis: Gene, Genome and Synthetic Biology

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De novo DNA synthesis is a powerful tool for DNA engineering and manipulating that is widely used in pharmaceutical and biotechnology industry. Advancement of chemical DNA synthesis and assembly underlies the recent breakthroughs of synthetic biology, which is expected as the next "hotspot" in post-genome era. However, despite these significant progresses in DNA manipulation, chemical genome synthesis and assembly remains a major challenge in genome engineering and synthetic biology.

In this study, we present a cost- and time- effective approach for genome synthesis. Two genomic DNA fragments were designed and generated based on a chemical synthesis process. The first one is a 50 kb human genome probe targeting on the Philadelphia Chromosome and the second one is full length human mitochondrial genome. By a combination of a scalable chmical synthesis process and a novel homologous DNA recombination approach, both genome sequences were synthesized, assembled and validated . Our data indicated a highly cost- and time- effective approach.

In summary, we established a genome synthesis platform that renders a fast generation of wild type and mutant genome and chromosome that indicates a widely implication in genetic diseases and personalized medicine. It indicates that *de novo* DNA synthesis from individual gene to genome becomes an important component of synthetic biology.

Jingjie Cui

Jingjie Cui received her Ph.D. in applied chemistry from South China University of Technology in 2009. Currently she is a post-doctoral fellow of the State Key Laboratory of Crystal Materials, Center of Bio & Micro/nano Functional Materials at the Shandong University. Her research interests are related to synthesis of nanomaterials, the application of nanomaterials in electrochemical biosensors and new energy sources.

Hong Liu

Hong Liu is a professor of materials in State Key Laboratory of Crystal Materials, Shandong University. He received his Ph.D. in materials from the Shandong University in 2001. His research interests are related to synthesis of nanomaterials, the application of nanomaterials in gas and biosensors, environmental protection, and new energy sources.

TiO_2 nanobelts electrode as a sensor for determination of anticancer drugs

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The purine analogues 6-thioguanine (6-TG), 6-O-benzylguanine (O-6-BG) and adenine phosphate (VB_4) are important anticancer therapeutic agents. 6-TG was reported non-electroactive, while the electrochemical behaviours of O-6-BG and VB_4 have not yet been reported. In this study, using TiO_2 nanobelts electrode as the work electrodes, we investigated the electrochemical behavior and kinetic characterization of the above anticancer drugs by various electrochemical techniques in a phosphate buffer solution of pH 7.4. The resulting chemically modified electrodes exhibited electrocatalytic activities in the oxidation of the anticancer drugs, including 6-TG, O-6-BG and VB_4. The irreversible oxidation peaks for three different anticancer drugs, 6-TG, O-6-BG and VB_4, can be clearly identified at +0.76, +0.65 and +0.89 V, respectively. The TiO_2 nanobelts are considered to be a promising candidate for biosensor applications of nucleic acid drugs that will be of significance to diagnostic medicine and molecular biology research.