# BIOGRAPHICAL SKETCH

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NAME

eRA COMMONS USER NAME (credential, e.g., agency login)

POSITION TITLE
Senior Investigator

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

| INSTITUTION AND LOCATION | DEGREE *(if applicable)* | COMPLETION DATE MM/YYYY | FIELD OF STUDY |
|---|---|---|---|
| Inner Mongolia Teachers' College for Nationalities, Tongliao, China | B.S. | 01/82 | Chemistry |
| University of Oklahoma, Norman, OK | Ph.D. | 12/90 | Chemistry |
| University of Maryland, Rockville, MD | Postdoc | 12/93 | Structural Biology |

## A. Personal Statement

I joined the ABL-Basic Research Program in 1995, moved to the Center for Cancer Research of the National Cancer Institute (NCI), National Institutes of Health (NIH) in 1999, and gained tenure in 2001 as an NIH Senior Investigator. At the NCI, I aim to provide a structural view of the reaction trajectory and/or functional cycle of selected biomolecular systems and to develop novel therapeutics using structure-based approach. My research has been focused on RNA biology, with an emphasis on RNA-processing proteins and RNA polymerase-associated transcription factors. I am also an educator with extensive experience in postgraduate education and training as well as classroom and workshop teaching.

## B. Positions, Scientific Appointments, and Honors

### Positions and Employment

| | |
|---|---|
| 1969-1972 | Medicine Practitioner, Zhaogen-Miao Village, Kailu County, Inner Mongolia, China |
| 1972-1975 | Teacher and Clinician, No. 8 High School, Tongliao, China |
| 1975-1978 | Teacher and Clinician, Teachers’ Training School, Tongliao, China |
| 1983-1985 | Teaching Assistant, Inner Mongolia Teachers' College for Nationalities, Tongliao, China |
| 1985-1990 | Research Assistant/Associate, University of Oklahoma, Norman, OK |
| 1991-1993 | Research Associate, University of Maryland, Rockville, MD |
| 1994-1995 | Research Assistant Professor, University of Maryland, Rockville, MD |

| | |
|---|---|
| 1995-1999 | Principal Investigator, ABL-Basic Research Program, National Cancer Institute, Frederick, MD |
| 1999-2001 | Principal Investigator, Center for Cancer Research, National Cancer Institute, Frederick, MD |
| 2001- | Senior Investigator, Center for Cancer Research, National Cancer Institute, Frederick, MD |

### Other Experience and Professional Memberships

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|---|---|
| 1986- | American Crystallographic Association |
| 1989- | National Honorary Chemical Society of America |
| 1994- | Society of Chinese Bioscientists in America |

### Honors/Awards

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|---|---|
| 1990 | Outstanding Graduate Research Award, University of Oklahoma |
| 1993 | Outstanding Postdoctoral Research Award, University of Maryland |
| 2003 | Wadsworth Lecturer, Wadsworth Center & State University of New York School of Public Health |
| 2003 | Ribo-Oncology Lecturer, University of Sherbrooke, Sherbrooke, Quebec, Canada |
| 2004 | Spotlight Recognition, National Cancer Institute at Frederick |
| 2008 | Appointment, United States Senior Biomedical Research Service (SBRS) |
| 2009 | Keynote Speaker, National Cancer Institute at Frederick and Fort Detrick “Chemistry as a Life Science” symposium |
| 2010 | Outstanding Science Award, Southeast Regional Collaborative Access Team |
| 2014 | Keynote Speaker, University of Maryland Molecular and Structural Biology Program Annual Retreat |
| 2015 | Rosetta Briegel Barton Lecturer, Department of Chemistry and Biochemistry, University of Oklahoma |
| 2016 | Planery Lecture, The 21st Biophysical Conference, Hsinchu, Taiwan |
| 2019 | Keynote Speaker, The 15th International Conference on Structural and Molecular Biology, Sydney, Australia, 2019. |
| 2019 | Molecular Horizons Lecturer, University of Wollongong, Wollongong, Australia, 2019. |

## C. Contributions to Science:

The Mechanism of dsRNA Processing by RNase III: How Dicer Dices

RNAi is mediated by siRNA and miRNA produced by members of the RNase III family. Representative members of the family include bacterial RNase III and eukaryotic Rnt1p, Drosha, and Dicer. For mechanistic studies, bacterial RNase III is a valuable model system for the family. We have determined crystal structures of bacterial RNase III in complex with various dsRNAs, revealing a stepwise mechanism for dsRNA processing. The structural information of protein-dsRNA interactions and the mechanism of dsRNA processing by bacterial RNase III have assisted the development of a new technology that uses an RNase III mutant to produce siRNA cocktails and helped elucidate the inside-out mechanism of Dicers from budding yeasts. We have also determined the crystal structure of yeast Rnt1p post-cleavage complex, the

first structure of a eukaryotic RNase III complexed with RNA in a catalytically meaningful manner. Strikingly, the N-terminal domain and dsRBD of Rnt1p function as two rulers for substrate selection. This unusual mechanism represents an example of the evolution of substrate selectivity and provides a framework for understanding the catalytic mechanism of eukaryotic RNase IIIs, including Drosha and Dicer. Cell, 124:355-366 (2006); Annu. Rev. Genet. 47:405-431 (2013); Molecular Cell, 54:431-444 (2014); WIREs RNA 10, e1521 (2019).

The Functional Cycle of Era: Implications for Ribosome Biogenesis

Era couples cell growth with cell division, and is, therefore, essential for cell viability. It contains an N-terminal GTPase domain and a C-terminal KH domain. Both domains are essential for function. However, the degree of interplay between the two domains, if any, was not known. We have characterized the functional cycle of Era by determining crystal structures of the protein at various functional states, providing the structural basis for its role in the maturation of 16S rRNA and assembly of the 30S ribosomal subunit. Present in nearly every bacterial species and essential for both cell growth and cell division, Era is unique among all other known protein functions of bacteria. Inhibition of Era function will likely stop the synthesis of bacterial ribosome. Therefore, Era is a potential target for the development of novel antibiotics to fight the worldwide crisis of antibiotic resistance. PNAS, 96:8396-8401 (1999); PNAS, 106:14843-14848 (2009); PNAS, 108:10156-10161 (2011); Advances in Biochemistry 62, 335-342 (2016).

The Crystal Structure of a Plectonemic RNA Supercoil: Implications for Viral RNA Packaging

Genome packaging is an essential housekeeping process in virtually all organisms for proper storage and maintenance of genetic information. Although the extent and mechanisms of packaging vary, the process involves the formation of nucleic-acid superstructures. Crystal structures of DNA coiled coils indicate that their geometries can vary according to sequence and/or the presence of stabilizers such as proteins or small molecules. However, such superstructures have not been revealed for RNA. We have determined the crystal structure of an RNA supercoil, which displays one level higher molecular organization than previously reported structures of DNA coiled coils. In the presence of the NusB protein from Aquifex aeolicus, two interlocking RNA coiled coils of double-stranded RNA, a "coil of coiled coils," form a plectonemic supercoil. Molecular dynamics simulations suggest that protein-RNA interaction is required for the stability of the supercoiled RNA. The supercoiled RNA in the crystal lattice has a nucleic acid density of 42 bp/100 nm3. Intriguingly, the average genome packing density of dsRNA viruses is ~40 bp/100 nm3. This study provides structural insight into higher-order packaging mechanisms of nucleic acids. Furthermore, the A. aeolicus NusB protein, given its sequence-independent interactions with supercoiled RNA, could potentially be utilized to promote the formation and/or crystallization of other nucleic-acid superstructures, or in the construction of novel nanostructures. Nat. Commun. 3:901 (2012).

The Reaction Trajectory of Pyrophosphoryl Transfer by HPPK, an Attractive Antibacterial Target

Folate co-factors are essential for life. Mammals obtain folates from their diet, whereas most microorganisms must synthesize folates de novo. Therefore, the folate biosynthetic pathway has been one of the principal targets for developing antimicrobial agents. 6-Hydroxymethyl-7,8-dihydropterin pyrophosphokinase (HPPK), which is not the target for existing antibiotics, catalyzes the transfer of pyrophosphate from ATP to 6-hydroxymethyl-7,8-dihydropterin (HP) to form AMP and 6-hydroxymethyl-7,8-dihydropterin pyrophosphate (HPPP). We have determined crystal structures of HPPK in complex with ATP-analog, with HP and ATP-analog, with HPPP and AMP, or with HPPP, revealing the reaction trajectory of HPPK-catalyzed pyrophosphoryl transfer. HPPK is not only an attractive target for developing novel antibiotics but also an excellent model system for studying the catalytic mechanism of enzymatic pyrophosphoryl transfer. Our studies of HPPK have provided important insights into the structure, dynamics, and catalytic mechanism of the enzyme. Using a structure- and mechanism-based approach, we have been developing a family of bisubstrate analogue inhibitors of HPPK as candidates for novel antibiotics. Two lead compounds have been identified for further

development. Structure, 8:1049-1058 (2000); Structure, 12:467-475 (2004); Bioorg. Med. Chem. 20:47-57 (2012); Bioorg. Med. Chem. 20:4303-4309 (2012); FEBS J. 281, 4123-4137 (2014).

The Reaction Trajectory of Glutathionyl Transfer by GST and Anticancer Prodrugs that Kills Cancer Cells from Within by Releasing Nitric Oxide

The GST superfamily of phase-II detoxification enzymes is derived from distinct gene classes denoted as alpha (A), mu (M), pi (P), etc. All GSTs catalyze the conjugation of the sulfur atom of glutathione (GSH) to an electrophilic center of endogenous or exogenous compounds, thereby increasing their aqueous solubility for subsequent excretion. Being ubiquitous and quite abundant in mammalian tissues, GSTs initiate the metabolism of a broad range of alkylating agents, and therefore play a central role in the detoxification of many carcinogens, as well as anticancer chemotherapeutic agents. Among the family members, GSTP is especially important in cancer therapy as it is often expressed at significantly higher levels in preneoplastic and neoplastic cells. It has also been shown that elevated levels of total GST and overexpression of GSTP often accompany the development of drug resistance in tumors of patients undergoing chemotherapy. Such factors have stimulated continued efforts to target GSTs as a primary objective in the discovery of anticancer agents. My postdoctoral research was focused on the mechanism of GST action. At the NCI, we have been trying to turn the GSTP-overexpression to the tumor's disadvantage by developing O2-aryl diazeniumdiolates (O2ADs) that release the established cytolytic agent nitric oxide (NO) upon metabolism by GSTP. This work has resulted in a structure-based lead compound, PABA/NO, for further development. Biochemistry, 32:12949-12954 (1993); Mol. Pharmacol. 65:1070-1079 (2004); J. Med. Chem. 49:1157-1164 (2006); Drug Des. Devel. Ther. 2:123-130 (2008); J. Med. Chem. 57:2292-2302 (2014); PLoS One 11(9):e0163821 (2016).