BIOGRAPHICAL SKETCH

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NAME: Song, Jikui

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

POSITION TITLE: Associate Professor of Biochemistry

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
University of Science and Technology of China, Hefei, Anhui	BS	07/1994	Chemical Physics
Institute of Biophysics, Chinese Academy of Sciences, Beijing	MS	07/1997	Molecular Biology
University of Wisconsin, Madison, WI	MS	12/2001	Computer Sciences
University of Wisconsin, Madison, WI	PHD	12/2002	Biochemistry
Memorial Sloan-Kettering Cancer Center, New York, NY	Postdoctoral Fellow	12/2011	Structural Biology and Epigenetics

A. Personal Statement

DNA methylation is an evolutionarily conserved epigenetic mechanism that critically regulates gene expression and cell lineage commitment. My long-term research interest focuses on understanding the mechanistic basis of mammalian DNA methylation and the relationship of its dysregulation to human diseases. In the past decade, I have carried out extensive structure-function characterizations of DNMT1-mediated maintenance DNA methylation and DNMT3A-mediated *de novo* DNA methylation. In addition, we delineated the structures and mechanisms of a number of pathogen-host interactions concerning both bacteria and viruses. I have published over 60 peer-reviewed articles, including recent publications in Nature, Nature Communications and Nature Structural & Molecular Biology.

1. Anteneh H, Fang J, **Song J**. Structural basis for impairment of DNA methylation by the DNMT3A R882H mutation. ***Nat. Commun*.** (2020) 11:2294.
2. Zhang ZM, Lu R, Wang P, Yu Y, Chen D, Gao L, Liu S, Ji D, Rothbart SB, Wang Y, Wang GG, **Song J**. Structural basis for DNMT3A-mediated de novo DNA methylation. ***Nature***. 2018; 554: 387-391.
3. Ren W, Lu J, Huang M, Gao L, Li D, Wang GG, **Song J**. Structure and regulation of ZCCHC4 in m^6A-methylation of 28S rRNA. ***Nat. Commun*.** (2019) 10: 5042.
4. Wang B, Thurmond S, Zhou K, Sánchez-Aparicio MT, Fang J, Lu J, Gao L, Ren W, Cui Y, Veit EC, Hong HJ, Evans MJ, O'Leary SE, Garcia-Sastre A, Zhou ZH, Hai R, **Song J**. Structural basis for STAT2 suppression by flavivirus NS5. ***Nat Struct & Mol Biol***. (2020) DOI: 10.1038/s41594-020-0472-y.

B. Positions and Honors

Positions and Employment

2002-2007 Assistant Researcher, University of Wisconsin, Madison, WI
2007-2010 Research Associate, Memorial Sloan-Kettering Cancer Center, New York, NY
2010-2011 Senior Research Scientist, Memorial Sloan-Kettering Cancer Center, New York, NY
2012-2017 Assistant Professor, Department of Biochemistry, University of California, Riverside, CA
2017-2020 Associate Professor, Department of Biochemistry, University of California, Riverside, CA
2020- Professor, Department of Biochemistry, University of California, Riverside, CA

Other Experiences and Professional Memberships

2012- Ad hoc Reviewer for *Scientific Reports, Biochemistry, Genes, PloS One, Protein & Cell, FEBS J, Plant Pathology, Epigenetics & Chromatin, Nucleic Acids Res, Structure, Cell Rep, J Am Chem Soc, Proc Natl Acad Sci USA, Science Advance, Nature Communications, Nature*.
2015- Member, Biophysical Society
2016- Member, American Society for Biochemistry and Molecular Biology
2017 Monitoring editor for *Proc Natl Acad Sci USA*
2018 Invited Speaker on Drug Discovery-2018
2020 Grant reviewer for NIH Director's Pioneer Award
2020 Invited Speaker on the Keystone Symposia, Cancer Epigenetics: New Mechanisms and Therapeutic Opportunities
2020- Member, Cancer Research Coordinating Committee, University of California

Honors

2013 Basil O'Connor Starter Scholar Research Award, March of Dimes Foundation
2013 Robert T. Poe Faculty Development Grant, Chinese American Faculty Association of Southern California
2013 Regents' Faculty Fellowship, University of California, Riverside
2014 Hellman Fellowship, Hellman Family Foundation
2015 Kimmel Scholar Award, Sidney Kimmel Foundation for Cancer

C. Contributions to Science

1. Uncover the structural basis of mammalian DNA and RNA methylation (2012-)

I have made major contributions in unravelling the structural basis of mammalian DNA and RNA methylation. During my postdoctoral training at Memorial Sloan-Kettering Cancer Center, I solved the first structure of DNMT1 in complex with hemimethylated CpG DNA, laying out the groundwork for mechanistic understanding of DNMT1-mediated maintenance DNA methylation. At UC Riverside, my lab determined the first structure of DNMT3A-DNA methylation complex, revealing the molecular basis for DNMT3A-mediated *de novo* DNA methylation. Furthermore, we explored the structural and functional consequence of DNMT3A R882H, a hot spot mutation implicated in Acute Myeloid Leukemia (AML), providing insights into the impairment of methylation by the DNMT3A R882H mutation in AML. In addition, we determined the structure of ZCCHC4, a novel m^6A RNA methyltransferase that specifically methylates 28S rRNA. Our work revealed an autoinhibitory mechanism by which the multiple domains of ZCCHC4 cooperate in 28S rRNA methylation, setting a new structure-function paradigm for m^6A RNA methyltransferases. These studies provided important insights into the dynamic establishment and maintenance of mammalian DNA and RNA methylation.

a. Anteneh H, Fang J, **Song J[#].** Structural basis for impairment of DNA methylation by the DNMT3A R882H mutation. ***Nat. Commun.*** (2020) 11:2294. [PMID: 32385248] ([#]Corresponding author)
b. Ren W, Lu J, Huang M, Gao L, Li D, Wang GG, **Song J[#].** Structure and regulation of ZCCHC4 in m^6A-methylation of 28S rRNA. ***Nat. Commun.*** 2019: (10): 5042. [PMCID: PMC6834594] ([#]Corresponding author)

c. Zhang ZM, Lu R, Wang P, Yu Y, Chen D, Gao L, Liu S, Ji D, Rothbart SB, Wang Y, Wang GG[#], **Song J**[#]. Structural basis for DNMT3A-mediated de novo DNA methylation. ***Nature*.** 2018; 554: 387-391. [PMCID: PMC5814352] ([#]Corresponding authors).
d. **Song J**, Teplova M, Ishibe-Murakami S, Patel DJ. Structure-based mechanistic insights into DNMT1-mediated maintenance DNA methylation. ***Science*.** 2012 Feb 10;335(6069):709-12. [PMCID: PMC4693633]

2. Decipher the functional regulation of mammalian DNA methylation (2011-)

Establishment and maintenance of mammalian DNA methylation is subjected to dynamic regulation in cells. I have investigated various regulatory mechanisms of the DNA methylation machinery. These studies have led to the identification of an autoinhibitory mechanism of DNMT1, which serves to discriminate hemimethylated over unmodified CpG DNA as substrates. Furthermore, my lab delineated the molecular recognition and conformational dynamics of two functional regulators in DNMT1-mediated maintenance DNA methylation: E3 ubiquitin ligase UHRF1 and deubiquitinase USP7. Through structural, biochemical and cellular analyses, we identified a mechanism by which the UHRF1-USP7 interaction allosterically regulates the conformational state and chromatin association of UHRF1, thereby shedding light onto their regulatory roles in maintenance DNA methylation. With a team of collaborators, we also developed DNA aptamer-based inhibitors against DNMT1. Intriguingly, one of the identified inhibitors binds and inhibits DNMT1 strongly, but shows no inhibitory activity toward DNMT3A/DNMT3B, serving as a novel scaffold for developing DNMT1-specfiic inhibitors. These studies not only provided important insights into the functional regulation of mammalian DNA methylation, but also opened up a window for development of novel therapeutic strategies targeting diseases involving aberrant DNA methylation.

a. Gao L, Tan XF, Zhang S, Wu T, Zhang ZM, Ai HW, **Song J**[#]. An intramolecular interaction of UHRF1 reveals dual control for its histone association. ***Structure*.** 2018; 26: 304-311. [PMCID: PMC580340] ([#]Corresponding author)
b. Zhang ZM, Rothbart SB, Allison DF, Cai Q, Harrison JS, Li L, Wang Y, Strahl BD, Wang GG, **Song J**[#]. An allosteric interaction links USP7 to deubiquitination and chromatin targeting of UHRF1. ***Cell Rep*.** (2015) 12:1400-6. [PMCID: PMC4558366] ([#]Corresponding author)
c. Wang L, Lee J, Gao L, Yin J, Duan Y, Jimenez LA, Adkins GB, Ren W, Li L, Fang J, Wang Y, **Song J**[#] and Zhong W[#]. A DNA aptamer for binding and inhibition of DNA methyltransferase 1. ***Nucleic Acids Res*.** 2019; 47(22):11527-11537. [PMCID: PMC7145629] ([#] Corresponding authors)
d. **Song J**, Rechkoblit O, Bestor TH, Patel DJ. Structure of DNMT1-DNA complex reveals a role for autoinhibition in maintenance DNA methylation. ***Science*.** 2011 Feb 25;331(6020):1036-40. [PMCID: PMC4689315]

3. Determine the molecular basis for pathogen-host interaction (2016-)

The interaction between virulence proteins and host defense factors critically influences the outcome of the battle between host and pathogen. With a team of collaborators, my lab determined the first crystal structures of YopJ family of bacterial effectors, a novel family of acetyltransferases that are produced by a broad range of Gram-negative bacteria. Through structural characterization of the substrate- and ligand-bound complexes of YopJ effectors, we identified a mechanism by which cofactor IP6 allosterically regulates the substrate binding and catalysis of YopJ effectors, providing a basis for understanding the structure-function relationship of this family of bacterial proteins. My lab also determined the crystal structures of full-length NS5 protein from Zika virus (ZIKV), which reveals conserved domain conformation among flavivirus NS5 proteins, and potential drug-binding site for allosteric inhibition. In addition, we delineated the structural basis for the complex between Epstein-Barr virus nuclear antigen 2 (EBNA2) and tumor suppressor BS69, which identified the BS69 C-terminal domains as an inhibitor of EBNA2. These studies provided a framework for future development of novel therapeutic strategies against bacterial and viral infections.

a. Zhang ZM, Ma K, Gao L, Hu Z, Schwizer S, Ma W[#], **Song J[#].** Mechanism of host substrate acetylation by a YopJ family effector. ***Nat. Plants***. (2017) 3:17115. [PMCID: PMC5546152] ([#]Corresponding authors)
b. Wang B, Tan XF, Thurmond S, Zhang ZM, Lin A, Hai R[#], **Song J[#].** The structure of Zika virus NS5 reveals a conserved domain conformation. ***Nat. Commun*.** (2017) 8:14763. [PMCID: PMC5378951] ([#]Corresponding authors)
c. Zhang ZM, Ma KW, Yuan S, Luo Y, Jiang S, Hawara E, Pan S, Ma W[#], **Song J[#].** Structure of a pathogen effector reveals the enzymatic mechanism of a novel acetyltransferase family. ***Nat. Struct. Mol. Biol.*** (2015) 10:1176-80. [PMID: 27525589] ([#]Corresponding authors)
d. Harter MR, Liu CD, Shen CL, Gonzalez-Hurtado E, Zhang ZM, Xu M, Martinez E, Peng CW[#], **Song J[#].** BS69/ZMYND11 C-terminal domains bind and inhibit EBNA2. ***Plos Pathog*.** (2016) 12(2): e1005414. [PMCID: PMC4742278] ([#]Corresponding authors)

4. Characterize the epigenetic readout of histone modifications (2009-)

Post-translational modification of histone proteins constitutes one of the major epigenetic mechanisms in gene regulation, and its misregulation contributes to an increasing number of human diseases. With a team of collaborators, I have identified novel regulatory mechanisms of key epigenetic players, including histone methyltransferases mixed lineage leukemia 1 (MLL1) and polycomb repression complex 2 (PRC2), and revealed how histone modification "readout" by effector proteins affects epigenetic signaling, leukemic transformation or Meier-Gorlin Syndrome. These studies established etiologic links between epigenetic regulation and human diseases. I served as the primary or co-investigator in all of these studies.

a. Zhang W, Sankaran S, Gozani O, **Song J[#]**. A Meier-Gorlin Syndrome mutation impairs the ORC1-nucleosome association. ***ACS Chem. Biol.*** (2015) 10:1176-80. [PMCID: PMC4654454] ([#]Corresponding author)
b. Wang GG, **Song J**, Wang Z, Dormann HL, Casadio F, Li H, Luo JL, Patel DJ & Allis CD (2009). Haematopoietic Malignancies Caused by Dysregulation of a Chromatin-binding PHD Finger. ***Nature*.** 459(7248): 847-51. [PMCID: PMC2697266]
c. Wang Z*, **Song J***, Milne TA, Wang GG, Li H, et al. Pro isomerization in MLL1 PHD3-bromo cassette connects H3K4me readout to CyP33 and HDAC-mediated repression. ***Cell*.** (2010) Jun 25;141(7):1183-94. [PMCID: PMC4690531] (**Equally contributing authors)*
d. Kuo A.J*., **Song J***, Cheung P*., Ishibe-Murakami S., Yamazoe S., Chen J.K., Patel D.J. & Gozani, O. (2012). ORC1 BAH domain links dimethylation of H4K20 to DNA replication licensing and Meier-Gorlin syndrome. ***Nature*.** 484(7392):115-9. [PMCID: PMC3321094] (**Equally contributing authors)*

Complete List of Published Work in MyBibliography: https://www.ncbi.nlm.nih.gov/myncbi/1-UWaaB0j7OQG/bibliography/public/

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

NIH/NIGMS
1R35GM119721 Song (PI) 08/01/2016-05/31/2021
Mechanistic Insights into Mammalian DNA Methylation
The goal of this project is to provide the mechanistic basis for the establishment, maintenance and regulation of mammalian DNA methylation.
Role: PI

NIH/NIAID
1R21AI147057 Song & Hai (PI) 7/1/2019 – 6/30/2021
Mechanistic understanding and inhibition of Zika NS5 protein
The goal of this project is to reveal the mechanistic basis of ZIKV NS5 protein and develop small-molecule inhibitor for enzymatic inhibition.
Role: PI (Multi PI: Rong Hai)

CV Information		
Last Name (Surname)	First Name	Middle Name or NMN (no middle initial)
Song	**Jikui**	

List all science and technology specialties that apply to your experience (e.g., materials sciences, battery technology, geosciences, fuel elements, waste management, etc.):

Structural Biology, Biochemistry, Biophysics, Molecular Biology

List dates in chronological order as MM/YYY for all work positions and all academic institutions attended (from age 18). Include the city, state/province, and country for each entry. If there is more than a 4-month date gap between entries, provide a brief explanation why no work or academic institutions were attended.

07/1988-07/1089 High School Student, No. 4 High School of Weihai, Shandong, China

09/1989-07/1994 Undergraduate Student, University of Science and Technology of China, Hefei

09/1994-07/1997 Graduate Student, Institute of Biophysics, Chinese Academy of Sciences, Beijing

08/1997-09/2002 Graduate Student, University of Wisconsin, Madison, WI

09/2002-10/2007 Assistant Researcher, University of Wisconsin, Madison, WI

11/2007-10/2010 Research Associate, Memorial Sloan-Kettering Cancer Center, New York, NY

11/2010-12/2011 Senior Research Scientist, Memorial Sloan-Kettering Cancer Center, New York, NY

01/2012-06/2017 Assistant Professor, Department of Biochemistry, University of California, Riverside, CA

07/2017-06/2020 Associate Professor, Department of Biochemistry, University of California, Riverside, CA

07/2020- Professor, Department of Biochemistry, University of California, Riverside, CA