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. I was trained with Dr. John L Markley for my PhD in protein structure and dynamics by NMR spectroscopy. My postdoctoral training with Dr. Dinshaw J Patel focuses on structural elucidation of protein complexes involved in epigenetic regulation. In the past decade, I have laid out the foundation for the proposed research by extensive structure-function characterizations of DNMT1-mediated maintenance DNA methylation and DNMT3A-mediated *de novo* DNA methylation. I have published over 70 peer-reviewed articles, including recent publications in Nature (in 2018, as corresponding author; in 2012, as co-first author; in 2009, as second author), Nature Communications (in 2017, 2019, 2020 and 2021, as corresponding author), Nature Structural & Molecular Biology (in 2016 and 2020, as corresponding author), Nature Plants (in 2017, as corresponding author), Cell Reports (in 2015 and 2016, as corresponding/co-corresponding author), Molecular Cell (in 2013, as co-corresponding author), Science (in 2011 and 2012, as first author) and Cell (in 2020, as co-author; in 2010, as co-first author). As an independent investigator at UC Riverside, I have had the opportunities of training seven postdoctoral researchers, nine graduate students and over a dozen undergraduate students. In summary, I have demonstrated a record of accomplished and productive research, and my expertise and experience have prepared me for a long-term endeavor in the areas of structural biology and DNA methylation.

Ongoing and recently completed projects that I would like to highlight include:
R35GM119721
Song (PI)
08/01/2016-05/31/2026
Mechanistic Insights into Mammalian DNA Methylation

1R01AI153419A
Hai (PI), Role: co-investigator
3/15/2021 – 2/28/2026
Mechanistic Insights into flavivirus NS5-mediated STAT2 Suppression

Citations:

1. Ren W, Fan H, Grimm SA, Guo Y, Kim, JJ, Li L, Petell CJ, Tan XF, Zhang ZM, Coan JP, Yin J, Gao L, Cai L, Khudaverdyan N, Çetin B, Patel DJ, Wang Y, Cui Q, Strahl BD, Gozani O, Miller KM, O'Leary SE, Wade PA, Wang GG, **Song J**. DNMT1 reads heterochromatic H4K20me3 to reinforce LINE-1 DNA methylation***. Nat Commun***. (2021) 12:2490. [PMID: 33941775]
2. 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]
3. Wang B, Thurmond S, Zhou K, Sánchez-Aparicio MT, Fang J, Lu J, Gao L, Ren W, Cui Y, Hong H, O'Leary SE, Garcia-Sastre A, Zhou ZH, Hao R, **Song J**. Structural basis for STAT2 suppression by flavivirus NS5. ***Nat Struct & Mol Biol.*** (2020) 20:875-885. [PMID: 32778820]
4. 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]

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

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
2017-	Professor, Department of Biochemistry, University of California, Riverside, CA
2016-	Member, American Society for Biochemistry and Molecular Biology
2020-	Member, American Association for the Advancement of Science
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. Wang B, Thurmond S, Zhou K, Sánchez-Aparicio MT, Fang J, Lu J, Gao L, Ren W, Cui Y, Hong H, O'Leary SE, Garcia-Sastre A, Zhou ZH[#], Hao R[#], **Song J[#]**. Structural basis for STAT2 suppression by flavivirus NS5. ***Nat Struct & Mol Biol.*** (2020) 20:875-885. [PMID: 32778820] ([#]Corresponding authors)
b. 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)
c. 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)
d. 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)

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. Fan H, Lu J, Guo Y, Li D, Zhang ZM, Tsai YH, Pi WC, A JH, Gong W, Xiang Y, Allison DF, Geng H, He S, Diao Y, Chen WY, Strahl BD, Cai L, **Song J[#]**, Wang GG[#]. BAHCC1 binds H3K27me3 via a conserved BAH module to mediate gene silencing and oncogenesis. ***Nat Genet.*** (2020) 52:1384-1396. [PMID: 33139953] ([#]Corresponding authors)
b. Ren W, Fan H, Grimm SA, Guo Y, Kim, JJ, Li L, Petell CJ, Tan XF, Zhang ZM, Coan JP, Yin J, Gao L, Cai L, Detrick B, Çetin B, Wang Y, Cui Q, Strahl BD, Gozani O, Miller KM, O'Leary SE, Wade PA, Patel DJ[#], Wang GG[#], **Song J[#]**. Direct readout of heterochromatic H3K9me3 regulates DNMT1-mediated maintenance DNA methylation. ***Proc Nat Acad Sci USA***. (2020) 117(31):18439-18447. [PMID: 32675241] ([#]Corresponding authors)

c. 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)*
d. 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)*

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