BIOGRAPHICAL SKETCH

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NAME: **CHENG, Xiaodong**

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

POSITION TITLE: **Professor of Epigenetics and Molecular Carcinogenesis**

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
Fudan University, Shanghai, China	B.Sc.	02/1982	Physics
State University of New York at Stony Brook	Ph.D.	11/1989	Neutron Protein Crystallography
Cold Spring Harbor Laboratory	Postdoctoral	12/1991	X-ray Protein Crystallography

A. Personal Statement

My work primarily focuses on generation, recognition, and erasure of epigenetic methyl marks on DNA and histones, which is the focus of this proposal. I have studied epigenetic methylation for the past 28+ years. My first publication on DNA methylation was in 1992 (Biochemistry). I was at Cold Spring Harbor Laboratory when I began a collaboration with Dr. Richard J. Roberts, that led to the discovery of DNA base flipping by HhaI DNA methyltransferase (1993 Cell; 1994 Cell; 1998 Nature Struct. Biol.).

In 1997, I moved to Emory University School of Medicine as Full Professor of Biochemistry, and my work in Emory focused on structural and functional linkage of DNA and histone methylation:

- Structure of PRMT3 - a protein arginine methyltransferase (2000 EMBO J)
- Structure of DNMT2 – a tRNA cytosine methyltransferase (2001 Nucleic Acids Res.)
- Structure of DIM5 - a histone lysine methyltrasnferase (2002 Cell)
- Structure of Dnmt3B PWWP domain binding DNA (2002 Nature Struct. Biol.)
- A Phe/Tyr switch mechanism controls degree of lysine methylation (me1/me2/me3) (2003 Mol. Cell)
- H3K9me3 is a mark for DNA methylation (2003 Nature Genetics)
- DNA adenine methyltransferases (Dam) (2003 Nature Struct. Biol.; 2005 Cell)
- ZnF UBP binds the C-terminal diglycine motif of unanchored ubiquitin (2006 Cell)
- BHC80 of LSD1 complex binds unmethylated H3 lysine 4 (H3K4me0) (2007 Nature)
- DNMT3L links H3K4me0 to *de novo* DNA methylation (2007 Nature)
- UHRF1 SRA domain recognizes hemi-methylated CpG via a base-flipping mechanism (2008 Nature)
- ERα regulation by SET7 (2008 Molecule Cell)
- G9a ankyrin repeat binds methylated histone H3 lysine 9 (H3K9me2/1) (2008 Nat. Struct. Mol. Biol.)
- G9a methylates non-histone protein substrates (2008 Nature Chem. Biol.)
- G9a Inhibition by a small molecule inhibitor BIX-01294 (2009 Nat. Struct. Mol. Biol.)
- PHF8 demethylase functions in reciprocal methylation of H3K4 and H3K9 (2010 Nat. Struct. Mol. Biol.)
- A methylation and phosphorylation switch in Dnmt1 (2011 NSMB) and NF-κB (2011 Nature Immunology)
- MPP8 interacts with Dnmt3a (DNA methylation) and G9a (H3K9 methylation) (2011 Nature Comm.)
- 5hmC in neurodevelopment and aging (2011 Nature Neuroscience) and in mESC (2013 Cell Reports)
- Zfp57 recognizes methyl-CpG within a specific DNA sequence (2012 Genes Dev.)
- Structure of a Tet-like dioxygenase in complex with 5-methylcytosine DNA (2014 Nature)
- Wilms tumor protein (WT1) binds 5-carboxylcytosine within a specific DNA sequence (2014 Genes Dev.)
- PRDM9 in complex with recombination hotspot DNA sequence (2016 Genes Dev.)
- Effector CD8 T cells dedifferentiate into long-lived memory cells (2017 Nature)

In 2017, I moved to MD Anderson Cancer Center, where I start to work on translational research, in addition to continue the basic research on epigenetic DNA and histone modifications:

- Structure of CTCF binding DNA (2017 Molecule Cell)
- ZFP568 for silencing a placental-specific growth factor (2017 Science; 2018 Cell)
- SETD3 as the first protein histidine methyltransferase (2019 Nature and 2019 Nature Communication)
- Structure of CcrM (cell-cycle regulated methylase) opens a DNA bubble (2019 Nature Communication)

- TRIM28-EZH2 interaction in cancer cells (2020 NAR Cancer)
- Dnmt3b3 regulates *de novo* DNA methylation activity (2020 Genes Dev.)
- ZNF410 represses fetal hemoglobin expression (2020 Molecule Cell)

Top 4 publications with the highest number of citations (as of 12/08/2020):

1. Ooi SK, Qiu C, Bernstein E, Li K, Jia D, Yang Z, Erdjument-Bromage H, Tempst P, Lin SP, Allis CD, **Cheng X**, Bestor TH (2007) DNMT3L connects unmethylated lysine 4 of histone H3 to de novo methylation of DNA. *Nature* **448**, 714-717 (PMC2650820) (992 citations)
2. Klimasauskas S, Kumar S, Roberts RJ, **Cheng X** (1994) *Hha*I methyltransferase flips its target base out of the DNA helix. *Cell* **76**, 357-69 (PMID: 8293469) (868 citations)
3. Schubert HL, Blumenthal RM, **Cheng X** (2003) Many paths to methyltransfer: a chronicle of convergence. *Trends Biochem. Sci*. **28**, 329-335 (PMC2758044) (566 citations)
4. Jia D, Jurkowska RZ, Zhang X, Jeltsch A, **Cheng X** (2007) Structure of Dnmt3a bound to Dnmt3L suggests a model for de novo DNA methylation. *Nature* **449**, 248-51 (PMC2712830) (545 citations)

B. Positions and honors

Positions and Employment

4/1/2017-present	The University of Texas MD Anderson Cancer Center: Professor of Epigenetics and Molecular Carcinogenesis (6/1/2019-) Professor of Molecular and Cellular Oncology (8/31/2016-5/31/2019) Program leader of Cancer Genetics and Epigenetics (CGE) of CCSG (07/01/2020-) Co-director of Center for Cancer Epigenetics (CCE) CPRIT Scholar in Cancer Research
8/31/2016-3/31/2017	Joint appointments in Emory University (51%) and MD Anderson Cancer Center (49%)
4/1/1997 – 3/31/2017	Emory University School of Medicine: Professor of Biochemistry and Georgia Research Alliance Eminent Scholar Adjunct professor of Chemistry and Physics
6/1/1990 – 3/31/1997	Cold Spring Harbor Laboratory: Senior Staff Investigator and W.M. Keck Foundation endowed professor (1994-1997) Staff Investigator (1992-1993) Robertson Postdoctoral Research Fellow (1990-1991)

Other Experience and Professional Memberships

Grant Reviewer:
NIH MSFA Study Section Regulation Member (2019-2025)
NIH MSFC Study Section (*Ad hoc* 02/2015; 10/2010; 02/2008)
NIH BBCB Study Section Regular Member (1997-2001);
Special Emphasis Panel/Scientific Review Group:
ZRG1-GGG-R(02) (11/16/2016); ZGM1 RCB-6 (10/2015); ZRG1 BCMB-D (02/2014);
NIEHS Target I Special Emphasis Panel (SEP): 03/2013
NIEHS Special Emphasis Panel of Environmental Influences on Epigenetic Regulation (2006);
NCI molecular oncology 3 cluster Review Committee (2006);
NCI site visit team for review of the Laboratory of Immunobiology (2003);
NCI initial review group (2001);
American Cancer Society: Genetic Mechanisms in Cancer Committee member (2005);
Army Breast Cancer Research Program (1995-1996)

Meeting Organizer and Session Chair
Session Chair at the Keystone symposia on DNA methylation (3/29-4/3, 2015)
FASEB Summer Methylation meeting:
co-organizer (2008) and session chairperson (2012, 2010, 2006, 2004, 2001);
Cold Spring Harbor Laboratory Banbury Center conference on “DNA base flipping: how and why”, 7-10 April 1996 (Co-organizer).

MD Anderson Committee member
G&E Steering committee (2020-2021)
Promotions & Tenure Committee (PTC) (09/01/2020-)
Technology Task Face (2020)
Service center committee (2020-present)
TMC3 Science Think Tank (2020)

Cancer Genetics and Epigenetics (CGE) of CCSG (07/01/202-)
UT System STAR program (2019-present)
Center for Cancer Epigenetics (co-director; 2018-present)
Keck Executive Committee (member at-large; 2017-present)
Core for Biomolecular Structure and Function (advisory; 2017-2020)
Emory University Committee member
BCDB Executive Committee (2012-2016)
Faculty Committee on Appointments and Promotions (2010-2012 and 1999-2001);
Chairperson of Biochemistry Structural Biology Faculty Search Committee (2006 and 2016);
Member of Chair search committee for Radiology Department (2003-2004);
Editorial Board member
Acting Executive Editor for *Epigenetics* (2020)
Epigenomes (2018-)
Genes & Development (2016-present)
Environmental Epigenetics (2015-present)
Epigenetics (2006-present)
Nucleic Acids Research (2002-present)
SER-CAT Executive Board (2017-present)
Board member and treasurer of Epigenetic Society (formerly DNA Methylation Society) (2005-present)

Honors

CPRIT Scholar in Cancer Research (2017-)
SER-CAT Outstanding Science Award (2015)
AAAS Fellow Elected (2012)
Albert E. Levy Awards for Excellence in Scientific Research (2008)
Georgia Research Alliance Eminent Scholar (1997-2016)

C. Contribution to Science: (total of 216 publications as of 12/2020) h-index=71 total citations >18,500
https://www.mdanderson.org/research/departments-labs-institutes/labs/cheng-laboratory/publications.html

1. Base flipping

Base flipping involves rotation of backbone bonds in double-stranded deoxyribonucleic acid (DNA) to expose an out-of-stack base, which can then be a substrate for an enzyme-catalyzed chemical reaction or for a specific protein binding interaction. The phenomenon was first observed for a DNA methyltransferase in 1994 (reference 1), and is now widespread for enzymes or proteins that require access to unpaired, mismatched, damaged or modified bases or even undamaged and unmodified bases for specific functions.

a. Klimasauskas S, Kumar S, Roberts RJ, **Cheng X** (1994) *Hha*I methyltransferase flips its target base out of the DNA helix. *Cell* **76**, 357-69 (PMID: 8293469)
The first example of the base flipping mechanism used by DNA base modification enzymes to access their targets

b. Jia D, Jurkowska RZ, Zhang X, Jeltsch A, **Cheng X** (2007) Structure of Dnmt3a bound to Dnmt3L suggests a model for de novo DNA methylation. *Nature* **449**, 248-51 (PMC2712830)
Illustrated the establishment of *de novo* DNA methylation by Dnmt3a-Dnmt3L complex

c. Hashimoto H, Horton JR, Zhang X, Bostick M, Jacobsen S, **Cheng X** (2008) The SRA domain of UHRF1 flips 5-methylcytosine out of the DNA helix. *Nature* **455**, 826-9 (PMC2602803)
The first example of a non-enzymatic DNA binding domain employing the base flipping mechanism for DNA recognition

d. Hashimoto H, Pais JE, Zhang X, Saleh L, Fu ZQ, Dai N, Corrêa IR, Zheng Y, **Cheng X** (2014) Structure of a Naegleria Tet-like dioxygenase in complex with 5-methylcytosine DNA. *Nature* **506**, 391-5 (PMC4364404)
The first structure of a DNA 5-methylcytosine (5mC) dioxygenase, which also uses the base-flipping mechanism to access the 5mC base, where successive oxidative modifications occur, resulting in 5-hydroxymethylcytosine (5hmC), 5-formylcytosine (5fC) and 5-carboxylcytosine (5caC).

2. Structures of AdoMet-dependent protein (arginine, lysine, histidine) methyltransferases

S-adenosyl-L-methionine (AdoMet or SAM) is the second most commonly used enzyme cofactor after ATP. The AdoMet-dependent methyltransferases act on a wide variety of target molecules, including DNA, RNA, proteins, polysaccharides, lipids, and a range of small molecules involved in metabolism. My group determined the first structure of a DNA methyltransferase (1993), the first structure of protein arginine methyltransferase

(2000), the first structure of a protein (histone) lysine methyltransferase (2002) and its complex with histone peptide substrate (2003), and the first structure of a protein histidine methyltransferase in complex with actin peptide (2018).

a. Zhang X, Zhou L, **Cheng X** (2000) Crystal structure of the conserved core of the protein arginine methyltransferase PRMT3. *EMBO J*. **19**, 3509-19 (PMC313989)
The first structure of a protein arginine methyltransferase

b. Zhang X, Tamaru H, Khan SI, Horton JR, Keefe LJ, Selker EU, **Cheng X** (2002) Structure of the Neurospora SET domain protein DIM-5, a histone H3 lysine methyltransferase. *Cell* **111**, 117-27 (PMC2713760)
The first structure of a protein (histone) methyltransferase

c. Zhang X, Yang Z, Khan SI, Horton JR, Tamaru H, Selker EU, **Cheng X** (2003) Structural basis for the product specificity of histone lysine methyltransferases. *Molecular Cell* **12**, 177-185 (PMC2713655)
Established a switch mechanism of Phe/Tyr (phenylalanine/tyrosine) in controlling the degree of lysine methylation by mono-, di- or tri-methylation.

d. Wilkinson AE, Diep J, Dai S, Liu S, Ooi YS, Song D, Li TM, Horton JR, Zhang X, Liu C, Trivedi DV, Ruppel KM, Vilches-Moure JG, Casey KM, Mak J, Cowan T, Elias JE, Nagamine CM, Spudich JA, **Cheng X***, Carette JE*, Gozani O* (2019) SETD3 is an actin histidine methyltransferase that prevents primary dystocia. *Co-corresponding authors. *Nature* **565**, 372-376 [NIHMSID 1515852]

3. Structural and functional crosstalk between DNA modification and histone methylation

Chromatin regulates transcriptional processes through postsynthetic modifications of both of its components: DNA and histones. Much remains to be learned about how the combination of these modifications (or lack thereof) facilitates or silences transcription. One broad theme has emerged that a web of interactions tightly coordinates the modification of a segment of DNA and its associated histones, affecting local chromatin structure and determining the functional states. We are the first to illustrate the mechanistic insights of anti-correlation of histone H3 lysine 4 (H3K4) methylaion and DNA methylation (2007), coordinated methylations of H3K9 and DNA (2011), inverse relationship between H3K4 and H3K9 methylation (2010). The crosstalk of different modifications also applies to non-histone proteins such as ERα (2008), NFκB (2011) and DNMT1 (2011).

a. Ooi SK, Qiu C, Bernstein E, Li K, Jia D, Yang Z, Erdjument-Bromage H, Tempst P, Lin SP, Allis CD, **Cheng X**, Bestor TH (2007) DNMT3L connects unmethylated lysine 4 of histone H3 to de novo methylation of DNA. *Nature* **448**, 714-717 (PMC2650820)
Revealed a novel mechanism of crosstalk between unmodified histone H3 lysine 4 (H3K4me0) and patterns of DNA methylation.

b. Collins RE, Northrop JP, Horton JR, Lee DY, Zhang X, Stallcup MR, **Cheng X** (2008) The ankyrin repeats of G9a and GLP histone methyltransferases are mono- and dimethyllysine binding modules. *Nature Struct. Mol. Biol.* **15**, 245-50 (PMC2586904)
Demonstrated that the ankyrin repeat domain is a reader domain that selectively binds to mono- and dimethylated lysine 9 of histone H3. A unique aspect of this finding is that these methyllysine-specific binding domains are found in G9a/GLP histone methyltransferases that produce these methyllysine marks, thus providing a mechanism for propagation of these marks by product binding.

c. Horton JR, Upadhyay AK, Qi HH, Zhang X, Shi Y, **Cheng X** (2010) Enzymatic and structural insights for substrate specificity of a family of jumonji histone lysine demethylases. *Nature Struct. Mol. Biol*. **17**, 38-43 (PMC2849977)
Provided an example of combinatorial readout of multiple covalent histone modifications of an activating histone mark (H3K4me3) read by a histone lysine demethylase PHF8, which subsequently removes repressive marks (H3K9me2).

d. Chang Y, Sun L, Kokura K, Horton JR, Fukuda M, Espejo A, Izumi V, Koomen JM, Bedford MT, Zhang X, Shinkai Y, Fang J, **Cheng X** (2011) MPP8 mediates the interactions between DNA methyltransferase Dnmt3a and H3K9 methyltransferase GLP/G9a. *Nature Commun*. **2**: 533 (PMC3286832)
Provides an example of crosstalk between DNA-modifying and histone-modifying enzymes.

4. Recognition of DNA modifications

a. Hashimoto H, Olanrewaju YO, Zheng Y, Wilson GG, Zhang X, **Cheng X** (2014) Wilms tumor protein recognizes 5-carboxylcytosine within a specific DNA sequence. *Genes Dev*. **28**, 2304-2313 (PMC4201290)
The first example of a transcription factor (WT1) binding DNA modification with 5-carboxylcytosine

b. Patel A, Horton JR, Wilson GG, Zhang X, **Cheng X** (2016) Structural basis for human PRDM9 action at recombination hot spots. *Genes Dev*. **30**(3): 257-265 (PMC4743056)
Illustrated an adaptability of PRDM9 to DNA sequence variations that in turn contributes to the variation in the locations and activities of meiotic recombination hot spots during meiosis.

c. Hashimoto H, Wang D, Horton JR, Zhang X, Corces VG, **Cheng X** (2017) Structural basis for the versatile and methylation-dependent binding of CTCF to DNA. *Mol. Cell* **66**(5): 711-720 (PMC5542067)
Explains the adaptability of CTCF tandem zinc-finger array to sequence variations and the position dependent effect of differential DNA methylation.

d. Patel A, Yang P, Tinkham M, Pradhan M, Sun M-A, Wang Y, Hoang D, Wolf G, Horton JR, Zhang X, Macfarlan T, **Cheng X** (2018) DNA conformation induces adaptable binding by tandem zinc finger proteins. *Cell* **173**(1): 221-233 (PMC5877318)
Evolutionary and structure-function dynamics of zinc finger-DNA interactions reveal unconventional recognition codes, and co-evolution of ZFP568 and its target gene Igf2 in mammals.

5. Small molecule inhibitors against epigenetic enzymes

a. Chang Y, Zhang X, Horton JR, Upadhyay AK, Spannhoff A, Liu J, Snyder JP, Bedford MT, **Cheng X** (2009) Structural basis for G9a-like protein lysine methyltransferase inhibition by BIX-01294. *Nature Struct. Mol. Biol.* **16**, 312-317 (PMC2676930)
The first structure of a histone lysine methyltransferase in complex with an inhibitor

b. Horton JR, Liu X, Gale M, Wu L, Shanks JR, Zhang X, Webber PJ, Bell JS, Kales SC, Mott BT, Rai G, Jansen DJ, Henderson MJ, Urban DJ, Hall MD, Simeonov A, Maloney DJ, Johns MA, Fu H, Jadhav A, Vertino PM, Yan Q, **Cheng X** (2016) Structural basis for KDM5A histone lysine demethylase inhibition by diverse compounds. *Cell Chem. Biol*. **23**(7): 769-81 (PMC4958579)
An extensive structural analysis that reveals how distinct inhibitor chemotypes bind KDM5 (a crucial oncogenic driver) and suggest avenues for improving KDM5 inhibitory potency and selectivity.

c. Horton JR, Liu X, Wu L, Zhang K, Shanks J, Zhang X, Rai G, Mott BT, Jansen DJ, Kales SC, Henderson MJ, Pohida K, Fang Y, Hu X, Jadhav A, Maloney DJ, Hall MD, Simeonov A, Fu H, Vertino PM, Yan Q, **Cheng X** (2018) Insights into the Action of Inhibitor Enantiomers against Histone Lysine Demethylase 5A. *J. Med. Chem*. **61**(7): 3193-3208 [NIHMSID 1002807]

d. Horton JR, Woodcock CB, Chen Q, Liu X, Zhang X, Shanks J, Rai G, Mott BT, Jansen DJ, Kales SC, Henderson MJ, Cyr M, Pohida K, Hu X, Shah P, Xu X, Jadhav A, Maloney DJ, Hall MD, Simeonov A, Fu H, Vertino PM, **Cheng X** (2018) Structure-based engineering of irreversible inhibitors against histone lysine demethylase KDM5A. *J. Biol. Chem*. **61**(23): 10588-10601 [NIHMSID 1002811]

D. Research Support

Ongoing Research Support

R35 GM134744-01 Cheng (PI) 01/01/2020-12/31/2024
Title: Epigenetic regulations of DNA and histone methylation and deMethylation: Structures and Mechanisms

CPRIT-RR160029 Cheng (PI) 04/01/2017 – 08/30/2021
Title: CPRIT Established Investigator Award

Recently Completed Research Support

R01 GM49245-24 Cheng (PI) 08/01/2014-07/31/2020
Title: DNA Methylation: Structures, Functions, and Regulation

R01-GM114306-03 Cheng (PI) 04/01/2015–03/31/2020
Title: Histone Lysine deMethylation: Structures, Inhibitions and Mechanisms

CURRICULUM VITAE

Xing Zhang

PRESENT TITLE AND AFFILIATION

Primary Appointment

Research Associate Professor, Department of Epigenet and Mol Carcinogenesis, The University of Texas MD Anderson Cancer Center, Houston, TX

Dual/Joint/Adjunct Appointment

N/A

CITIZENSHIP

United States

OFFICE ADDRESS

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6767 Bertner Ave
Unit Number: 1000
Houston, TX 77030
Room Number: BSRB Room S9.8336,
Phone: 713-745-6303
Email: xzhang21@mdanderson.org

EDUCATION

Degree-Granting Education

Fudan University, shanghai, China, BS, 1985, Microbiology

SUNY Stony Brook, Stony Brook, NY, PHD, 1995, Genetics

Postgraduate Training

N/A

CREDENTIALS

Board Certification

N/A

Licensures

Active

N/A

Inactive

N/A

EXPERIENCE/SERVICE

Academic Appointments

Research Assistant Professor of Biochemistry, Emory University School of Medicine, Atlanta, GA, 1997-2016

Research Associate Professor, Department of Molecular and Cellular Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, 10/13/2016-present

Administrative Appointments/Responsibilities

N/A

Other Appointments/Responsibilities
N/A

Endowed Positions
N/A

Consultantships
N/A

Military or Other Governmental Service
N/A

Institutional Committee Activities
N/A

HONORS AND AWARDS
N/A

RESEARCH
Grants and Contracts
Funded
Co-PI, Epigenetic regulations of DNA and histone methylation and deMethylation: Structures and Mechanisms, R35 GM134744-01, NIH/NIGMS, 01/01/2020-12/31/2024

$361,000direct + $223820 indirect=$584,820 total)

Co-PI, 50%, DNA Methylation: Structures, Functions, and Regulation, 5R01-GM049245-24, NIH/NIGMS, 8/1/2014-7/31/2019 (note: no-cost extension 8/1/2018-7/31/2020)

($312,761 direct + $184,667 indirect=$497,428 total)

Pending

Completed
Co-PI, 50%, Histone Lysine deMethylation: Structures, Inhibitions and Mechanisms, 1R01GM114306-03, NIH/NIGMS, 4/1/2015-3/31/2019

($194,641 direct + $115,729 indirect=$310,370 total)

Co-Principal Investigator, Histone Lysine Methylation: Structures and Functions, 2R01 GM068680-08, NIH/NIGMS, 6/1/2009-5/31/2013, $865,421 ($216,355/year)

Co-Principal Investigator, DNA Methylation: Structures, Functions, and Regulation, 2R01 GM049245-20, NIH/NIGMS, 8/30/2010-7/31/2014, $983,838 ($247,500/year)

Not Funded
N/A

Protocols
Funded
N/A

Unfunded
N/A

Patents and Technology Licenses
Patents
N/A

Technology Licenses

N/A

Grant Reviewer/Service on Study Sections

N/A

PUBLICATIONS

Peer-Reviewed Original Research Articles

1. Cheng X, **Zhang X**, Pflugrath JW, Studier FW (1994) The structure of bacteriophage T7 lysozyme, a zinc amidase and an inhibitor of T7 RNA polymerase. *Proc. Natl. Acad. Sci. USA*. **91**(9): 4034-8.
2. **Zhang X**, Studier FW (1995) Isolation of transcriptionally active mutants of T7 RNA polymerase that do not support phage growth. *J. Mol. Biol*. **250**(2): 156-68.
3. **Zhang X**, Studier FW (1997) Mechanism of inhibition of bacteriophage T7 RNA polymerase by T7 lysozyme. *J. Mol. Biol*. **269**(1): 10-27.
4. M. O'Gara, **X. Zhang**, R. J. Roberts, X. Cheng (1999) Structure of a binary complex of *Hha*I methyltransferase with S-adenosyl-L-methionine formed in the presence of a short nonspecific DNA oligonucleotide. *J. Mol. Biol.* **287**, 201-210.
5. **Zhang X**, Zhou L, Cheng X (2000) Crystal structure of the conserved core of the protein arginine methyltransferase PRMT3. *EMBO J*. **19**, 3509-19.

   This was the first structure of a Protein Arginine (R) Methyltransferase

6. A. Dong, J. A. Yoder, L. Zhou, **X. Zhang**, T. Bestor, X. Cheng (2001) Structure of human DNMT2, an enigmatic DNA methyltransferase homologue that displays denaturant-resistant binding to DNA. *Nucleic Acids Res*. **29**, 439-448.
7. J. R. Horton, K. Sawada, M. Nishibori, **X. Zhang**, X. Cheng (2001) Two polymorphic forms of human histamine methyltransferase: structural, thermal and kinetic comparisons. *Structure,* 837-849.
8. **Zhang X**, Tamaru H, Khan SI, Horton JR, Keefe LJ, Selker EU, Cheng X (2002) Structure of the Neurospora SET domain protein DIM-5, a histone H3 lysine methyltransferase. *Cell* **111**, 117-127.

   This was the first structure of a Protein Lysine Methyltransferase
   Accompanied by minireview: T. O. Yeates (2002) Structures of SET domain proteins: protein lysine methyltransferases make their mark. *Cell* 111, 5-7.

9. C. Qiu, K. Sawada, **X. Zhang**, X. Cheng (2002) The PWWP domain of mammalian DNA methyltransferase Dnmt3b defines a new family of DNA-binding folds. *Nature Struct. Biol*. **9**, 217-224.
10. D. M. Green, K. A. Marfatia, E. B. Crafton, **X. Zhang**, X. Cheng, A. H. Corbett (2002) Nab2p is required for poly(A) RNA export in *Saccharomyces cerevisiae* and is regulated by arginine methylation via Hmt1p. *J. Biol. Chem*. **277**, 7752-7760.
11. Y.-H. Lee, S. S. Koh, **X. Zhang**, X. Cheng and M. R. Stallcup (2002) Synergy among nuclear receptor coactivators: selective requirement for protein methyltranferase and acetyltransferase activities. *Mol. Cell. Biol*. 22, 3621-3632.
12. **Zhang, X**, Cheng, X (2003) Structure of the predominant protein arginine methyltransferase PRMT1 and analysis of its binding to substrate peptides. *Structure* **11**, 509-520.
13. J. Min, **X. Zhang**, X. Cheng, S. I. S. Grewal, R. Xu (2002) Structure of the SET domain histone lysine methyltransferase Clr4. *Nature Struct. Biol*. 9, 828-832.

14. S. E. Whitehead, K. W. Jones, **X. Zhang**, X. Cheng, R. M. Terns, M. P. Terns (2002) Determinants of the interaction of the spinal muscular atrophy disease protein SMN with the dimethylarginine-modified box H/ACA small nucleolar ribonucleoprotein GAR1. *J. Biol. Chem*. 277, 48087-48093.
15. **Zhang X**, Yang Z, Khan SI, Horton JR, Tamaru H, Selker EU, Cheng X (2003) Structural basis for the product specificity of histone lysine methyltransferases. *Molecular Cell* **12**, 177-185.
    This was the first structure of a ternary complex between a histone lysine MTase, its cofactor Ado-Met and substrate peptide.
    Previewed by: R. N. Dutnall (2003) Cracking the histone codes: one, two, three methyls, you're out! *Molecular Cell* 12, 3-4.
16. H. Tamaru, **X. Zhang**, D. McMillen, P. Singh, J. Nakayama, S. I. Grewal, C. D. Allis, X. Cheng, E. U. Selker (2003) Trimethylated lysine 9 of histone H3 is a mark for DNA methylation in Neurospora crassa. *Nature Genetics*, 34, 75-79.
17. P. Wu, C. Qiu, A. Sohail, **X. Zhang**, A. S. Bhagwat, X. Cheng (2003) Mismatch repair in methylated DNA: structure and activity of the mismatch-specific thymine glycosylase domain of methyl-CpG-binding protein MBD4. *J. Biol. Chem*. 278, 5285-5291.
18. Z. Yang, J. R. Horton, L. Zhou, Xu Jia Zhang, A. Dong, **X. Zhang**, S. L. Schlagman, V. Kossykh, S. Hattman, X. Cheng (2003) Structure of the bacteriophage T4 DNA adenine methyltransferase. *Nature Struct. Biol*. 10, 849-855.
19. Jackson JP, Johnson L, Jasencakova Z, Zhang X, PerezBurgos L, Singh PB, Cheng X, Schubert I, Jenuwein T, Jacobsen SE. (2004) Dimethylation of histone H3 lysine 9 is a critical mark for DNA methylation and gene silencing in Arabidopsis thaliana. *Chromosoma*. 112, 308-315
20. A. Dong, L. Zhou, **X. Zhang**, S. Stickel, R.J. Roberts, X. Cheng (2004) Structure of the Q237W mutant of HhaI DNA methyltransferase: an insight into protein-protein interactions. *Biological Chemistry* 385, 373-379
21. **Zhang X**, Studier FW (2004) Multiple roles of T7 RNA polymerase and T7 lysozyme during bacteriophage T7 infection. *J. Mol. Biol*. **340**(4): 707-30.
22. K. Sawada, Z. Yang, J.R. Horton, R.E. Collins, **X. Zhang**, and X. Cheng (2004) Structure of the conserved core of the Yeast Dot1p, a nucleosomal histone H3 lysine79 methyltransferase. *J. Biol. Chem*. 279, 43296-43306 (Epub July 29, 2004).
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95. Mohamed Mahgoub, Jacob Paiano, Melania Bruno, Wei Wu, Sarath Pathuri, **Xing Zhang**, Sherry Ralls, Xiaodong Cheng, Andre Nussenzweig, Todd Macfarlan. Dual Histone Methyl Reader ZCWPW1 Facilitates Repair of Meiotic Double Strand Breaks. [Posted October 29, 2019]
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Invited Articles

N/A

Editorials

N/A

Other Articles

N/A

Abstracts

N/A

Book Chapters

Cheng X, Hashimoto H, Horton JR, **Zhang X** (2010) Mechanisms of DNA methylation, methyl-CpG recognition, and demethylation in mammals. In: Handbook of Epigenetics: The New Molecular and Medical Genetics (Trygve Tollefsbol, editor). Oxford: Academic Press (ISBN: 978-0-12-375709-8) (DOI: 10.1016/B978-0-12-375709-8.00002-2) pp 9-24

Books (edited and written)
N/A

Letters to the Editor
N/A

Manuals, Teaching Aids, Other Teaching Publications
N/A

Other Publications
N/A

EDITORIAL AND REVIEW ACTIVITIES

Editor/Service on Editorial Board(s)
N/A

Member of Editorial Review Board
N/A

Journal Reviewer
N/A

Other Editorial and Review Activities
N/A

TEACHING

Teaching Within Current Institution -

Formal Teaching

Courses Taught
N/A

Training Programs
N/A

Other Formal Teaching
N/A

Supervisory Teaching

Committees

Advisory Committees
N/A

Supervisory Committees
N/A

Examining Committees
N/A

Direct Supervision

Undergraduate and Allied Health Students
N/A

Medical Students
N/A

Graduate Students
N/A

Postdoctoral Research Fellows
N/A

Clinical Residents and Fellows
N/A

Other Supervisory Teaching
N/A

Teaching Outside Current Institution
Formal Teaching
Courses Taught
N/A

Training Programs
N/A

Other Formal Teaching
N/A

Supervisory Teaching
Committees
Advisory Committees
N/A

Supervisory Committees
N/A

Examining Committees
N/A

Direct Supervision
Undergraduate and Allied Health Students
N/A

Medical Students
N/A

Graduate Students
N/A

Postdoctoral Research Fellows
N/A

Clinical Residents and Fellows
N/A

Other Supervisory Teaching
N/A

CONFERENCES AND SYMPOSIA
Organization of Conferences/Symposia (Include chairing session)
N/A

Presentations at National or International Conferences
Invited
N/A

Other, Including Scientific Exhibitions
March 10—16, 2003, Speaker, Keystone Symposia: The Enzymology of Chromatin and Transcription, Santa Fe, New Mexico
Organizer(s) Shelley L. Berger and Jerry L. Workman

Seminar Invitations from Other Institutions
N/A

Lectureships and Visiting Professorships
N/A

Other Presentations at State and Local Conferences
N/A

PROFESSIONAL MEMBERSHIPS/ACTIVITIES
Professional Society Activities, with Offices Held
National and International
N/A

Local/State
N/A

UNIQUE ACTIVITIES
N/A

DATE OF LAST CV UPDATE
1/17/2020

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors. Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Gundeep Kaur

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

POSITION TITLE: Postdoctoral Fellow

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*)*	END DATE MM/YYYY	FIELD OF STUDY
Kurukshetra University, India	B.Sc.	07/2008	Biotechnology
ICAR-National Dairy Research Institute, India	M.Sc.	06/2011	Animal Biochemistry
CSIR-Institute of Microbial Technology (CSIR-IMTech), India	Ph.D.	04/2018	Biophysics
University of Oxford, UK	Newton Bhabha Fellow	09/2016	Structural Biology
Baylor College of Medicine, USA	Postdoctoral Associate	06/2019	Structural Biology
UT MD Anderson Cancer Center, USA	Postdoctoral Fellow	Present	Structural Biology

A. Personal Statement

I have a broad background in biophysics and biochemistry with specific training and expertise in protein biochemistry, X-ray crystallography and structure-function studies of protein-protein complexes involved in transcription and epigenetics. As an undergraduate, I was able to conduct research with Dr. MS Chauhan, where I learnt techniques like In Vitro Maturation (IVM), In Vitro Fertilization (IVF), In Vitro Culture (IVC) of buffalo oocytes/embryos, mammalian cell/tissue culture techniques and latest molecular biology techniques. As a master's student with Dr. Suresh Atreja, my research project focused on Comparative Analysis of Apoptotic Features in Fresh and Cryopreserved Buffalo (*Bubalus bubalis*) Spermatozoa. As a predoctoral student with Dr. Krishan Gopal, my research focused on the regulation of transcription in pathogenic bacteria (*Mycobacterium tuberculosis*), primarily on characterizing the structural and functional studies on RNA polymerase (RNAP) and RNA Polymerase binding proteins. During the course of my Ph.D., I was exposed to a variety of methods that underline the multi-disciplinary nature of modern research in structural biology. My research involved extensive use of cloning, expression, purification of recombinant bacterial proteins and multi subunit protein-protein complexes and their biophysical characterization, molecular docking, molecular dynamics simulations, homology modelling and structural characterization. I developed a novel protocol for the purification of large bacetrial transcription complexes. I was first author of the several research papers. I have solved the X-ray crystal structure of one the essential transcription regulators from pathogenic bacteria, *Mycobacterium tuberculosis (Mtb)* and cryo-EM structure of bacterial RNAP. During my

undergraduate and graduate careers, I received several academic and teaching awards. For my postdoctoral training, my research interest is focused in the field of epigenetics. My sponsor Dr. Xiaodong Cheng, is an internationally recognized leader in the epigenetics and DNA methylation and has an extensive record for training postdoctoral fellows. I have a proven record of successfully collaborating with other researchers, and producing peer-reviewed publication.

a. Yang Zeng*, Ren Ren*, Gundeep Kaur*, Swanand Hardikar, Zhengzhou Ying, Lance Babcock, Esha Gupta, Xing Zhang, Taiping Chen, Xiaodong Cheng. The inactive Dnmt3b3 isoform preferentially enhances Dnmt3b-mediated DNA methylation. Genes and Development. 2020; 34;1546-1558 (*: Equal contribution).
b. Gundeep Kaur, Soni Kaundal, Srajan Kapoor, Jonathan M. Grimes, Juha T. Huiskonen and Krishan Gopal. Mycobacterium tuberculosis CarD, an essential transcription regulator forms amyloid-like fibrils. Nature Scientific Reports. 2018; 8: 10124.
c. Gundeep Kaur, Srajan Kapoor, Soni Kaundal, Dipak Dutta and Krishan Gopal Thakur. Structure-Guided Designing and Evaluation of Peptides Targeting Bacterial Transcription. Frontiers in Bioengineering and Biotechnology. 2020; 8:797.

B. Positions and Honors

Positions and Employment

2011-2012	Research Intern, CSIR-IMTech, India
2012-2014	Junior Research Fellow, CSIR-IMTech, India
2014-2017	Senior Research Fellow, CSIR-IMTech, India
2016	Newton Bhabha Fellow, University of Oxford, UK
2018-2019	Postdoctoral Associate, Baylor College of Medicine, USA
2019-Present	Postdoctoral Fellow, UT MD Anderson Cancer Center, USA

Other Experience and Professional Memberships

2019-	American Society of Microbiology
2019 -	Electron Microscopy Society of India
2019 -	Texas Medical Center PostDoctoral Association
2020 -	American Crystallography Association

Honors

2003	'Antriksh Pari' Kalpana Chawla award
2003	Certificate of Merit in Science awarded by Central Board of Secondary Education, India
2005-2008	Merit scholarship, B.Sc
2008	Roll of Honour, B.Sc.
2009-2011	Junior Research Fellowship awarded by ICAR-NDRI, India
2011	Gold Medalist, M.Sc. Animal Biochemistry
2011-2012	Diamond Jubilee "Research Interns" Award awarded by CSIR-IMTech, India
2012-2017	INSPIRE Fellowship awarded by Department of Science and Technology, India
2016	Newton Bhabha Fellowship at Wellcome Trust Centre for Human Genetics, University of Oxford, UK awarded by British Council, UK and Department of Science and Technology, India

C. Contribution to Science

1. **Early Career:** My early career contributions were focused on comparative analysis of apoptotic features in fresh and cryopreserved buffalo (*Bubalus bubalis*) spermatozoa. More specifically, I worked with a team of veterinarians at the ICAR-NDRI to develop novel cryoprotectants and extenders could be used for cryopreserving the buffalo semen.

a. Gundeep Kaur* and S.K. Atreja*. Early Detection of Buffalo Sperm Apoptosis at various stages of Cryopreservation. International Advanced Research Journal in Science, Engineering and Technology. 2018; 5:5056 (*: corresponding author)

2. **Graduate Career:** My graduate research contributions focused on transcriptional gene regulation in pathogenic bacteria, Mycobacterium tuberculosis *(Mtb)*. I characterized (structurally as well as functionally) few RNA polymerase/transcription factor protein-protein interactions that would eventually help in delineating the molecular processes governing the survival, drug tolerance and virulence of the pathogenic bacteria. My Ph.D. research was focused on the structural and functional studies on RNA polymerase and RNA Polymerase binding proteins. The interaction between RNAP and RNAPBP (CarD) is necessary for the survival and pathogenesis of *Mtb*, and the interface between CarD/RNAP has also been proposed as a novel and a potential drug target. I designed a novel protocol for purifying large bacterial protein-protein transcription complexes. I solved the crystal structure of CarD and confirmed the presence of the homo-dimeric state in solution. Further, I discovered that CarD has a propensity to form higher-order oligomers and amyloid fibrils in solution, which compromises its DNA binding and transcription activation properties. Based on these finding I proposed a plausible mechanism of transcription regulation under stress conditions in *Mtb*. In order to disrupt the CarD/RNAP interface, I used an interface peptide-based strategy and designed a set of peptides capable of disrupting mycobacterial transcription. Using molecular docking and in vitro transcription assays, I demonstrate that one of the designed peptides inhibits mycobacterial transcription with IC_{50}~50 μM. I solved the first high resolution 3.75 Å solution structure of bacterial RNAP using single particle cryo-EM. In addition, I performed preliminary studies to characterize HelD, an RNABP from Bacillus subtilis *(Bsub*) alone and in complex with *Bsub* RNAP. Also, I was also involved in additional projects where I was involved in characterizing bacterial toxin and immunity pair protein systems.

a. Gundeep Kaur, Dipak Dutta, and Krishan Gopal Thakur. Crystal structure of Mycobacterium tuberculosis CarD, an essential RNA polymerase binding protein, reveals a quasi domain-swapped dimeric structural architecture. Proteins Structure, Function and Bioinformatics. 2014; 82:879.
b. Gundeep Kaur, Soni Kaundal, Srajan Kapoor, Jonathan M. Grimes, Juha T. Huiskonen and Krishan Gopal. Mycobacterium tuberculosis CarD, an essential transcription regulator forms amyloid-like fibrils. Nature Scientific Reports. 2018; 8: 10124.
c. Gundeep Kaur, Srajan Kapoor and Krishan Gopal. Bacillus subtilis HelD, an RNA polymerase interacting helicase, forms amyloid-like fibrils. Frontiers in Microbiology. 2018; 9:1934.
d. Gundeep Kaur, Srajan Kapoor, Soni Kaundal, Dipak Dutta and Krishan Gopal Thakur. Structure-Guided Designing and Evaluation of Peptides Targeting Bacterial Transcription. Frontiers in Bioengineering and Biotechnology.2020; 8:797.

e. Soni Kaundal, AmarDeep, Gundeep Kaur and Krishan Gopal Thakur. Molecular and Biochemical Characterization of YeeF/YezG, A Polymorphic Toxin-Immunity Protein Pair from *Bacillus subtilis.* Frontiers in Microbiology. *2020; 11:13.*

3. **Postdoctoral Career:** As a postdoctoral fellow, my research is focused on studying the structural and functional effects of epigenetic modifications in DNA and histones. My research interests have been focused on determining the structures of players of epigenetics (reader, writer and erasers) carrying out DNA modification, deciphering their mechanism of action and determining their role in various cancers.
    a. Janani Kumar, Gundeep Kaur, Ren Ren, Yue Lu, Kevin Lin, Jia Li, Yun Huang, Anamika Patel, Michelle C Barton, Todd Macfarlan, Xing Zhang, Xiaodong Cheng KRAB domain of ZFP568 disruptsTRIM28 mediated abnormal interactions in cancer cells. Nucleic Acid Research Cancer. 2020; 2;2.
    b. Yang Zeng*, Ren Ren*, Gundeep Kaur*, Swanand Hardikar, Zhengzhou Ying, Lance Babcock, Esha Gupta, Xing Zhang, Taiping Chen, Xiaodong Cheng. The inactive Dnmt3b3 isoform preferentially enhances Dnmt3b-mediated DNA methylation. Genes and Development. 2020; 34;1546-1558 (*: Equal contribution).