OMB No. 0925-0001 and 0925-0002 (Rev. 10/15 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH

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NAME: Brian David Strahl

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

POSITION TITLE: Professor of Biochemistry and Biophysics; Faculty Director of the UNC High-Throughput Peptide Synthesis and Arraying Facility

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 |
| --- | --- | --- | --- |
| Univ. of North Carolina at Greensboro, NC | B.A. | 09/88-06/93 | Chemistry and Biology |
| North Carolina State University, NC | Ph.D. | 08/93-06/98 | Biochemistry |
| University of Virginia, VA | Postdoc | 08/98-12/01 | Biochemistry and Molecular Genetics |

A. Personal Statement

I have had a long-standing desire to understand how histone post-translational modifications (PTMs) regulate chromatin structure and function, and, particularly how dysregulation of these modifications causes diseases such as cancer. As a postdoc with David Allis, I identified and characterized the first lysine-specific histone methyltransferases. Also, Dr. Allis and I set forth the Histone Code Hypothesis, a compelling concept regarding the functions of histone PTMs that has led the epigenetic research field for nearly two decades. My lab at UNC has added many additional seminal discoveries as to how histone modifications regulate chromatin. For example, we found that a variety of enzymes and histone chaperones (*e.g*., Set2, Rad6/Bre1, Spt6) associate with RNA polymerase II to organize chromatin and control gene transcription. We have also developed a high-throughput proteomics platform containing “Histone Code” peptide arrays to decipher how histone modifications, and the codes they generate, regulate recruitment of chromatin proteins that govern the diverse functions associated with DNA. This platform has defined the histone interactions of numerous single and paired “reader” domains in chromatin-associated proteins, and, further, the platform has enabled determination of the functions of many of the interactions we discovered. For example, we recently defined the molecular basis of UHRF1’s role in DNA methylation maintenance and the role of TAF14’s YEATS domain in transcriptional regulation.

**B. Positions and Honors**

**Professional Positions**

* 1. Graduate Research

Department of Biochemistry, North Carolina State University (advisor: William L. Miller)

* 1. Postdoctoral Fellow

Department of Biochemistry and Molecular Genetics, University of Virginia School of Medicine (advisor: C. David Allis)

2002-2008 Assistant Professor

Department of Biochemistry and Biophysics, University of North Carolina School of Medicine

2003-present Member of the UNC Lineberger Comprehensive Cancer Center

2008-present Associate Professor

Department of Biochemistry and Biophysics, University of North Carolina School of Medicine

2010-present Faculty Director, Peptide Synthesis and Arraying Core Facility, UNC

2014-present Professor

Department of Biochemistry and Biophysics, University of North Carolina School of Medicine

2015-present Co-Director, Program in Chromatin and Epigenetics, University of North Carolina

2016-present Vice Chair

Department of Biochemistry and Biophysics, University of North Carolina School of Medicine

**Honors and Awards**

1. Recipient of the American Institute of Chemists Foundation award for outstanding scholarship

in chemistry.

1998 Recipient of the Becton-Dickinson award for outstanding research in Biochemistry (from Ph.D.).

* 1. National Institutes of Health NRSA postdoctoral fellowship award

2002 Recipient of a UNC Research Council Award

2003 Recipient of a Presidential Early Career Award for Scientists and Engineers (PECASE); sponsored by NIGMS

2004 Pew Scholar (Pew Scholars Program in the Biomedical Sciences)

2005 Recipient of the ASBMB Schering-Plough Research Institute Award for outstanding research

contributions to biochemistry and molecular biology

2005 Recipient of the North Carolina State University Outstanding Alumnus Award

2006 Recipient of the University of North Carolina at Greensboro Young Alumni Award

2006 Named as a Jefferson-Pilot Fellow in Academic Medicine, UNC

2008 Recipient of an Exceptional, Unconventional Research Enabling Knowledge Acceleration (EUREKA) award

2009 Recipient of the Ruth and Phillip Hettleman Prize for Artistic and Scholarly Achievement, UNC

2018 Named an Oliver Smithies Investigator, UNC

2018 Recipient of UNC’s Excellence in Basic Science Mentoring Award

**Other Professional Experience**

2005 *Ad-hoc* review panel member for MG-C Study Section, NIH

2006 *Ad-hoc* review panel member for NIDA Study Section, NIH

2008 *Ad-hoc* reviewer for the Fungal Genetics Special Emphasis Panel, NIH

2009-present Editorial board member of *Molecular and Cellular Biology*

2012 *Ad-hoc* reviewer for the NIH transformative research award initiative (Special Emphasis Panel ZRG1 BCMB-A), NIH

2012 *Ad-hoc* reviewer for theNIH Director’s Early Independence Award (Special Emphasis PanelZRG1 BBBP-E), NIH

2013-present Editorial board member of *Epigenetics & Chromatin*

2014 *Ad-hoc* review panel member for MG-A Study Section, NIH

2015 *Ad-hoc* reviewer for Special Emphasis Panel ZRG1 GGG F(80) for R15 applications, NIH

2015 *Ad-hoc* review panel member for MG-A Study Section, NIH

2015-present Editorial board member of *Journal of Biological Chemistry*

2016 *Ad-hoc* reviewer for Special Emphasis Panel ZRG1 GGG F(80) for R15 applications, NIH

2016-2020 Review panel member for MG-A Study Section, NIH

C. Contributions to Science

**1.** Contributed to the launch of the histone lysine methylation field. As a postdoctoral fellow with Dr. David Allis, I pioneered the discovery of the first enzymes responsible for histone lysine and arginine methylation (*i.e*., Set2, Set1, SUV39H1 and PRMT1). I also pioneered the development of antibodies directed against the methyl groups of histone lysine and arginine residues (α-H3K9me2, α-H3K4me2 and α-H4R3me2). These reagents and my biochemical characterizations showed that histone methylation is fundamental in regulating chromatin organization and gene activity. With Dr. Allis, I also put forward the Histone Code Hypothesis, a highly influential review that galvanized the chromatin community into determining how histone modifications are interpreted and how they function. The Histone Code review has been cited over 6000 times.

1. **Strahl, B. D.**, Ohba, R., Cook, R. G. & Allis, C. D. (1999). Methylation of histone H3 at lysine 4 is highly conserved and correlates with transcriptionally active nuclei in *Tetrahymena*. *Proc. Natl. Acad. Sci. USA* **96**:14967-14972. PMCID: PMC24756
2. **Strahl, B. D.** & Allis, C. D. (2000). The language of covalent histone modifications. *Nature* 403:41-45. PMCID: PMC4099259.
3. Rea, S., Eisenhaber, F., O’Carroll, D., **Strahl, B. D.**, Sun, Z-W, Opravil, S., Schmid, M., Mechtler, K., Ponting, C., Allis, C. D. & Jenuwein, T. (2000). Regulation of chromatin structure by site-specific histone H3 methyltransferases. *Nature* **406**:593-599. PMID: 10949293
4. **Strahl, B. D.**\*, Briggs, S. D.\*, Brame, C. J., Caldwell, J. A. Koh, S., Ma, H., Cook, R. G., Shabanowitz, J., Hunt D. F., Stallcup, M. R. & Allis, C. D. (2001) Methylation of histone H4 at arginine 3 occurs in vivo and is mediated by the nuclear receptor coactivator PRMT1. *Current Bio.* **11**:996-1000. PMID: 11448779

**2.** Contributed to understanding of H2B ubiquitylation in gene transcription and in the ‘*trans*’*-*histone regulatory pathway. We demonstrated that histone H2B ubiquitylation (H2Bub1) is fundamental for regulating the outcome of both H3K4 methylation (H3K4me) and H3K79 methylation (H3K79me), thus explaining fundamentally how histones ‘cross-talk’. We also showed that H2Bub1 is a histone mark that tracks in the coding region of genes and is required for transcription elongation. We explained how H2Bub1 is connected to the transcription elongation process by showing that the Rad6/Bre1 complex associates with the PAF complex and elongating RNA polymerase II (RNAPII), and that the BUR kinase (P-TEFb) contributes to transcriptional regulation through the establishment of H2Bub1 and histone methylation. We also revealed how Bre1 is tightly regulated across the genome to mediate precise control of H2Bub1 levels that impact gene regulation.

1. Briggs, S. B., Xiao, T., Sun, Z.-W., Caldwell, J. A., Shabanowitz, J., Hunt, D. F., Allis, C. D. & **Strahl, B. D.** (2002)Trans-histone regulatory pathway in chromatin. *Nature* **418**:498. PMID: 12152067.
2. Laribee, R. N., Krogan, J. N., Xiao, T., Shibata, Y., Hughes, T. R., Greenblatt, J. F., **Strahl, B. D.** (2005) BUR kinase selectively regulates H3 K4 trimethylation and H2B ubiquitylation through recruitment of the PAF elongation complex. *Current Bio*. 15:1487-1493. PMCID: PMC1851578.
3. Xiao, T. Kao, C. F., Krogan, N., Sun, Z.-W., Greenblatt, J. F., Osley, M. A., **Strahl, B. D.** (2005) Histone H2B ubiquitylation is associated with elongating RNA polymerase II. *Mol Cell Biol.* 25:637-651. PMID: 15632065.
4. Wozniak, G. G. & **Strahl, B. D.** (2014) Catalysis-dependent stabilization of Bre1 fine-tunes histone H2B ubiquitylation to regulate gene transcription. *Genes and Development*. 28:1647-1652. PMCID: PMC4117940.

**3.** Discovered Set2-mediated H3K36 methylation and determined the function of this modification. In David Allis’ lab, I discovered Set2 as a H3K36 nucleosomal-specific methylase that mediates transcriptional repression. In defining the role of this enzyme and its modification, we showed that Set2 associates with the C-terminal domain of the elongating form of RNAPII, and Set2 deposits its mark in the transcribed regions of genes. Further work defined a new domain that directs Set2’s interaction with RNAPII, and it determined that H3K36me functions in transcription elongation. With Jack Greenblatt and Steve Buratowski, we showed that H3K36me recruits the Rpd3S histone deacetylase complex to remove transcription-linked histone acetylation upon passage of RNAPII. The inability to erase this histone acetylation causes pervasive, spurious transcription. We are now deciphering how the Set2 enzyme itself is regulated and defining new roles for H3K36me. As an example, we recently showed that Set2/H3K36me regulates the DNA damage response and contributes to DNA repair, and Set2 is regulated at the level of protein stability.

1. Xiao, T., Hall, H., Kizer, K. O., Shibata, Y., Hall, M. C., Borchers, C. H. & **Strahl, B. D.** (2003) Phosphorylation of RNA polymerase II CTD regulates H3 methylation in yeast. *Genes & Dev.* 17:654-663. PMCID: PMC196010.
2. Jha, D. K. & **Strahl, B. D.** (2014) H3K36 methylation regulates chromatin remodeling and checkpoint activation after DSB. *Nature Commun.* 5:3965. PMID: 24910128.
3. McDaniel, S. L., Hepperla, A., Huang, Jie, Kulkarni, V. G., Davis, I. J. & **Strahl, B. D.** (2017) H3K36 Methylation Regulates Nutrient Stress Response in Saccharomyces cerevisiae by Enforcing Transcriptional Fidelity. *Cell Reports*. 19:2371-2382. PMCID: PMC5528882.
4. Dronamraju, R., Jha, D., Eser, E., Dominguez, D., Adams, A., Choudhury, R., Chiang, Y. C., Rathmell, W. K., Emanuele, M. J., Churchman, L. S. & **Strahl, B. D.** (2018) Set2 methyltransferase facilitates cell cycle progression by maintaining transcriptional fidelity. *Nucleic Acids Res* 46:1331-1344.

**4.** Defined how the histone chaperone Spt6 contributes to RNAPII CTD phosphorylation and function. Spt6 is an H3/H4 histone chaperone that associates with the elongating form of RNAPII and re-deposits histones in the wake of transcription. Without functional Spt6, histones are not properly deposited and cryptic transcription prevails across the genome. Significantly, the chaperone Spt6 also regulates Set2-mediated H3K36 methylation. To understand how Spt6 contributes to H3K36 methylation, we uncovered a new mode of regulation in transcription elongation. Specifically, Spt6 regulates the establishment of a feed-forward circuit that controls Ctk1-mediated serine 2 phosphorylation (Ser2P) on the CTD, thereby controlling Set2 methylation. This circuit is controlled by the PAF transcription elongation complex, which recruits Spt6 to genes. Thus, our studies have connected Spt6’s transcription elongation function to its regulation of Ser2P CTD phosphorylation that promotes H3K36me and other elongation-related events dependent on Ser2P (*e.g*., mRNA 3’-end processing).

1. Youdell, M. J.\*, Kizer, O. K.\*, Kisseleva-Romanova, E. Fuchs, S. M., Duro, E., Korn, K., **Strahl,B. D.** & Mellor, J. (2008) Spt6 controls methylation of lysine 36 on histone H3 to stabilize transcribed chromatin. *Mol Cell Biol.* 16:4915-4926. PMCID: PMC2519698.
2. Dronamraju, R. & **Strahl B. D.** (2014) A feed forward circuit comprising Spt6, Ctk1 and PAF regulates Pol II CTD phosphorylation and transcription elongation. *Nucleic Acids Research*. 42(2):870-881. PMCID: PMC3902893.
3. Dronamraju, R., Hepperla, A. J., Shibata, Y., Adams, A. T., Magnuson, T., Davis, I. J. & **Strahl, B. D.** Spt6 association with RNA Polymerase II directs mRNA turnover during transcription. (2018) *Molecular Cell*. 21:1054-1066. PMID: 29932900.
4. Dranamraju, R., Kerschner, J. L., Peck, S. A., Patel, D., Aslam, S., Mosley, A. L. & **Strahl, B. D.** ­­Casein Kinase II Phosphorylation of Spt6 Enforces Transcriptional Fidelity by Maintaining Spn1-Spt6 Interaction. *Cell Reports*. 25:3476-3489.

**5.** Developed a novel platform to decipher the Histone Code and defined new rules of chromatin engagement. To further understand how histone modifications signal chromatin-associated processes, we developed a histone peptide microarray platform containing hundreds of histone peptides covering all of the major histones and variants that are combinatorially modified with distinct PTMs. We have engaged in a multitude of collaborations to characterize novel reader domains in chromatin-associated proteins, and we have been dissecting how single and ‘paired’ reader domains in these proteins engage multiple histone PTMs (*i.e*., combinatorial readout and cross-talk). Using this platform, we recently made several insightful discoveries into the function of the E3 ubiquitin ligase UHRF1; we showed that UHRF1 ‘reads’ a pattern of histone and DNA PTMs to regulate the recruitment and stability of DNMT1, thereby promoting the DNA methylation maintenance pathway. Finally, we have used our arrays as quality control devices to resolve critical issues surrounding histone antibodies in use by the scientific community.

1. Rothbart, S. B., Krajewski, K., Nady, N., Tempel, W., Xue, S., Badeaux, A. I., Barsyty-Lovejoy, D., Martinez, J. Y., Bedford, M. T., Fuchs, S. M., Arrowsmith, C. H. & **Strahl, B. D**. (2012) Association of UHRF1 with H3K9 methylation directs the maintenance of DNA methylation. *Nature Structural & Molecular Biology*. 19:1155-1162. PMCID: PMC3492551.
2. Rothbart, S. B., Dickson, B. M., Ong, M. S., Krajewski, K., Houliston, S., Kireev, D. B., Arrowsmith, C. H. & **Strahl, B. D.** (2013) Multivalent histone engagement by the linked tandem Tudor and PHD domains of UHRF1 is required for the epigenetic inheritance of DNA methylation. *Genes & Development*. 27:1288-1298. PMCID: PMC3690401.
3. Rothbart, S. B., Dickson, B. M., Raab, J. R., Grzybowski, A. T., Krajewski, K., Guo, A. H., Shanle, E. K., Josefowicz, S., Z., Fuchs, S. M., Allis, C. D., Magnuson, T. R., Ruthenburg, A. J., **Strahl, B. D.** (2015) An interactive database for the assessment of histone antibody specificity. *Molecular Cell* 59:502-511. PMCID: PMC4530063.
4. Shanle, E. K, Andrews, F. H., Meriesh, H., McDaniel, S. L., Dronamraiu, R., DiFiore J., Jha, D., Wozniak, G. G., Bridgers, J., Kerschner, J. L., Martín, G. M., Morrison A. J., Krajewski, K., Kutateladze, T. \* & **Strahl, B. D.** \* (2015) Association of Taf14 with acetylated histone H3 directs gene transcription and the DNA damage response and. *Genes & Development*. 29:1795-1800. PMCID: PMC4573853.

Full list of Dr. Strahl’s publications are listed in:

<https://www.ncbi.nlm.nih.gov/sites/myncbi/brian.strahl.1/bibliography/51770080/public/?sort=date&direction=ascending>

D. Research Support

**Ongoing Research Support**

1R35GM126900-01 (PI: Strahl) 5/01/18 – 4/30/23

National Inst. of Health

**Mechanisms of chromatin and transcriptional regulation**

*This MIRA award provides support to our ongoing studies into the role of histone PTMs in chromatin regulation.*

1 R01 CA198482-01(PIs: Davis, Rathmell, Strahl) 9/15/15 – 8/14/20

National Inst. of Health

**Chromatin maintenance in cancer progression**

*This proposal seeks to understand the role of mutated SETD2 in the progression of renal cell carcinomas.*

R21 CA216673 (PI, Frye, Strahl) 9/01/17 – 8/31/19

*National Inst. of Health*

**Modulating the DNA methylation program through UHRF1 antagonism**

*The goal of this proposal is therefore is to discover potent, selective, cell-active antagonists of the histone and*

*DNA binding domains of UHRF1.*

T32-CA009156 (PI, Der) 7/1/80 – 7/31/21

National Inst. of Health

**Integrated Training in Cancer Model Systems**

*The goal of this project is to support the research and career training of postdoctoral fellows in cancer biology.*

Not Assigned (Margolis) 1/1/17 – 12/31/20

Qura Therapeutics LLC

**QURA - Project 2 - Round 2 - Immune Modulation and Clearance of HIV Infection**

*The purpose of this research is the development of therapies leading to an HIV Cure.*

**Completed Research Support**

1 R01 DA036897-01 (PIs: Duronio, Matera, Strahl)

National Inst. of Health

**Engineering histone genes to interrogate the epigenetic code in space and time**

*These studies aim to test the role of post-translationally modified histone residues in animal development.*

1 R01 DA036877-01 (PIs: Kuhlman and Hahn)

National Inst. of Health

**Spatiotemporal Control of the Epigenome via Photoactivatable Nuclear Localization**

*We aim to explore a light-inducible switch in yeast and mammalian cells target histone modifies to regulate chromatin structure and function.*

Role: Collaborator

1 R01 GM110058-01 (PI: Strahl)

National Inst. of Health

**Factors that regulate chromatin organization and gene transcription**

*This proposal aims to elucidate the fundamental mechanisms by which Spt6 contributes to the maintenance of chromatin structure in the coding and regulatory regions of the genome.*

1 R01 GM068088-12A1 (PI: Strahl)

National Inst. of Health

**Role of Set2 and H3 methylation in chromatin function**

*The goal of this proposal is to study the function of histone H3 methylation and demethylation at lysine 36 in transcriptional regulation and the cell cycle.*

Award Number 1330320 (PI: Strahl)

National Science Foundation

**Role of Dot1 and H3K79 methylation in gene regulation**

*The goal of this project is to uncover the fundamental mechanisms by which Dot1 functions in cellular biology.*

W.M. Keck Foundation (PI: Waters)

**New Tools for Characterization of the Protein Methylome and the Histone Code**