BIOGRAPHICAL SKETCH

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NAME: Peggy J Farnham

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

POSITION TITLE: Professor and Chair, Department of Biochemistry and Molecular Medicine,
Interim Director of the USC Norris Comprehensive Cancer Center

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
Rice University, Houston, TX	B.A.	05/78	Biochemistry
Yale University, New Haven, CT	Ph.D.	05/82	Mol.Biophys.&Biochem
Stanford University, Stanford, CA	Postdoc	12/86	Molecular Biology

A. Personal Statement

I have been a leader in the genome-wide study of mammalian transcription factors by developing technologies that combine chromatin immunoprecipitation with genomic microarray hybridization (ChIP-chip assays) and with high throughput sequencing (ChIP-seq). My lab was the first to develop ChIP protocols for mammalian cells and for the study of tumors from cancer patients, focusing on key cancer pathways regulated by E2F, MYC, and β-catenin. I have been a member of the ENCODE Consortium, the NIH Roadmap Epigenome Mapping Consortium, and the PsychENCODE Consortium. As part of these consortia, my lab has been a major contributor to the production of ChIP-seq datasets in normal and tumor cells for site-specific factors, histone-modifying complexes, and modified histones, developing protocols that are widely used by the field. In addition to bench work, my lab has developed programs to assist in the analysis of genome-scale ChIP-chip and ChIP-seq data and to derive consensus motifs from experimentally identified binding sites. Current projects in my lab are focused on oncogenic transcription factors, the identification and characterization of cancer-associated enhancers, and epigenomic regulation of cancer cell phenotypes. We have expertise in genome engineering, employing genomic nucleases and artificial transcription factors based on zinc finger, TALEN, and CRISPR platforms. My contributions to technology development and genome-wide analyses have been recognized by appointment an AAAS Fellow and by receiving the ASBMB Herbert A. Sober Award for outstanding biochemical and molecular biological research. The Web of Science catalogs 182 of my publications and reports a current h-index of 71; over the last 10 years my publications have been cited an average of 1539 times/year with 2884 citations in 2017 and a total of 28,892 citations.

Examples of publications due to my involvement in genomic and epigenomic consortia

(a) The ENCODE Project Consortium. Identification and analysis of functional elements in 1% of the human genome by the ENCODE pilot project. **Nature** 447: 799-816, 2007. PMID: 17571346. PMC2212820.
(b) THE ENCODE CONSORTIUM. An Integrated Encyclopedia of DNA Elements in the Human Genome. **Nature** 489:57-74, 2012. PMID:22955616.
(c) Roadmap Epigenome Mapping Consortium. Integrative analysis of 111 reference human epigenomes. **Nature**, 518:317-330, 2015. PMID:25693563
(d) The PsychENCODE Project, **Nature Neuroscience** 18:1707-1712, 2015. PMID:26605881.

B. Positions and Honors

Positions

1982-83: Damon Runyon-Walter Winchell Postdoc. Fellow, Genetics Dept, Stanford Univ., Stanford, CA
1983-86: NIH Postdoctoral Fellow, Dept. of Biological Sciences, Stanford Univ., Stanford, CA

1987-92: Assistant Professor, McArdle Laboratory for Cancer Research, Univ. of Wisconsin, Madison, WI
1992-97: Associate Professor, McArdle Laboratory for Cancer Research, Univ. of Wisconsin, Madison, WI
1996-01: Chair, Graduate Program in Cellular and Molecular Biology, Univ. of Wisconsin, Madison, WI
1997-04: Professor, McArdle Laboratory for Cancer Research, Univ. of Wisconsin, Madison, WI
2004-10: Professor, Pharmacology, Univ. of California, Davis, CA
2005-10: Associate Director of Genomics, UC Davis Genome Center
2011-present: William Keck Professor of Biochemistry, Norris Cancer Center, USC, Los Angeles, CA
2013-2015: Associate Dean of Graduate Affairs, Keck School of Medicine USC, Los Angeles, CA
2014-present: Leader, Epigenetics and Regulation Program, Norris Cancer Center, USC, Los Angeles, CA
2015-present: Chair, Department of Biochemistry and Molecular Medicine, USC, Los Angeles, CA
2017-2018: Interim Associate Director of Basic Sciences, Norris Cancer Center, USC, Los Angeles, CA
2018-present: Interim Director of the USC/Norris Comprehensive Cancer Center, USC, Los Angeles, CA

Other Experience and Professional Memberships
Member: AAAS, ASM, ASBMB, and AACR
Secretary, American Society of Biochemistry and Molecular Biology, 2004-2006
Member, Editorial Board, Journal of Biological Chemistry, 1996-2001
Associate Editor of Journal of Biological Chemistry, 2001-2006
Member, Editorial Board, Molecular and Cellular Biology, 1998-2006
Member, Editorial Board, Genome Research, 2008-2014
Member, Molecular Cytology Study Section, NIH, 1994-1998
Ad hoc reviewer, Molecular Biology Study Section, NIH
2004-2018: Member of NHGRI-sponsored ENCODE Consortium
2008-2015: Member of NIH Roadmap Reference Epigenome Mapping Centers
2013-present: Member of NIH-sponsored PsychENCODE Consortium

Honors
NIH Predoctoral Fellow, 1978-1982
Damon Runyon-Walter Winchell Postdoctoral Fellow, 1982-1983
NIH Postdoctoral Fellow, 1983-1986
Elected as AAAS Fellow in 2010
Appointed William M Keck Endowed Professor in 2011
ASBMB Herbert A. Sober Award in 2012; for outstanding biochemical and molecular biological research, with particular emphasis on development of methods and techniques to aid in research

Patents
United States Patent 7,129,328 10/31/06
United States Patent 7,220,844 05/22/07

C. Contributions to Science

1. Technology development: One of my major contributions to science has been the development of new technological approaches. At several times in my career, it has become clear that a new approach was needed to answer a research question. For example, as a graduate student, my project was to address the molecular mechanisms involved in the process of transcriptional attenuation in the tryp operon. I developed a base analog in vitro transcription system that provided new insights into the role of DNA-DNA and RNA-DNA interactions in transcriptional regulation. As a postdoc, I realized that the biochemistry of transcriptional regulation of mammalian genes was at a standstill because the current in vitro system worked only for viral promoters having a strong TATA box. Therefore, I developed the first in vitro transcription assay system for non-TATA box mammalian promoters. Extending upon this work after setting up my own lab, I developed a luciferase-based reporter transient transfection assay system to allow the study of cell cycle regulation of mammalian promoters. We used this system to make the key discoveries that E2F and MYC cooperate to control progression into S phase of the cell cycle. The next big technological barrier that I encountered was the need to examine DNA-protein interactions at an endogenous promoter under physiological conditions. To do so, my lab developed the first ChIP assay for mammalian cells and then extended this technology to develop the first ChIP-chip assay for mammalian cells (Weinmann et al, 2002). Our first ChIP-chip assays were based on CpG island arrays spotted with PCR fragments. Although this technology was seen as major advance, it was clear that the ChIP assay needed to be extended beyond promoters. Therefore, in collaboration with NimbleGen Systems, I developed a

method by which high density oligonucleotide arrays could be used for human ChIP-chip studies. My lab then moved into ChIP-seq and developed protocols and programs for this new technology. We have used ChIP-seq of artificial zinc finger transcription factors to show that the zinc finger platform has thousands of off target binding events and thus may not be optimal for genomic engineering or gene therapy (Grimmer et al. 2014). Our most recent technological developments include the use of CRISPR/Cas9 genomic nucleases to delete enhancers from the human genome (Yao et al. 2014) and the creation of epigenetic toggles switches (O'Geen et al. 2017).

(a) Weinmann AS, Yan PS, Oberley MJ, Huang HMT, **Farnham PJ**. Isolating human transcription factor targets by combining chromatin immunoprecipitation and CpG microarray analysis. **Genes & Development** 16:235-244,2002. PMC155318. This manuscript provides the first demonstration that ChIP-chip can be used with human cells; given a "must read" ranking at Faculty of 1000: F1000.com/11799066.

(b) Grimmer MR, Stolzenburg S, Ford E, Lister R, Blancafort P, **Farnham PJ**. Analysis of an artificial zinc finger epigenetic modulator: widespread binding but limited regulation. **Nucleic Acids Research** 42:10856-10868, 2014. PMID:25122745. This manuscript provides the first genome-wide ChIP-seq analysis of an artificial zinc finger epigenetic regulator.

(c) Yao L, Tak YG, Berman BP, **Farnham PJ**. Functional annotation of colon cancer risk SNPs. **Nature Communications** 5:5114, 2014. PMID: 25268989. This manuscript describes one of the first uses of CRISPR/Cas9 genomic nucleases to delete an enhancer from the human genome.

(d) O'Geen H, Ren C, Nicolet CM, Perez AA, Halmai J, Le VM, Mackay JP, **Farnham PJ**, Segal DJ. dCas9-based epigenome editing suggests acquisition of histone methylation is not sufficient for target gene repression. **Nucleic Acids Research** 45(17):9901-9916, 2017.PMID:28973434. This manuscript describes the creation and use of a variety of epigenetic toggle switches that can repress gene expression.

2. Insights into transcriptional regulation by oncogenic transcription factors: My early work focused on understanding transcription networks involving the E2F and MYC family of oncogenic transcription factors. I published ~50 corresponding author primary research articles concerned with these transcriptional regulators. My lab was the first to show that E2F1 and MYC cooperate to push cells through G1/S phase by regulating distinct groups of target genes. We identified the first E2F and MYC target genes, which were involved in purine (*dhfr*) and pyrimidine (*cad*) biosynthesis, respectively. We began our genome-wide studies of E2F1 by developing ChIP-chip for mammalian cells, but rapidly progressed to ChIP-seq. Importantly, we used ChIP-seq to show that the great majority of E2F1 binding sites do not contain an E2F consensus motif but instead co-localize with chromatin-bound RNA Polymerase II (Bieda et al. 2006). We followed that with a novel ChIP-seq analysis of mutant E2F1 proteins, demonstrating that the DNA binding domain of E2F1 is necessary and sufficient for E2F1 to be recruited to in vivo binding sites, even those that lack a consensus motif. In our studies of MYC, we showed that MYC activates the *cad* promoter via a post-RNA Polymerase II recruitment mechanism, interacting with P-TEFb to stimulate a bound, but paused, RNA polymerase II (Eberhardy and Farnham, 2002). This was the first demonstration that MYC regulates transcription by release of pausing. We have also used CRISPR/Cas9 genomic nucleases to study Myc regulation, deleting an enhancer that regulates MYC, resulting in downregulation of hundreds of MYC target genes (Tak et al. 2016). We have recently begun study of ZFX, a transcription factor associated with poor patient survival in many different cancers. Our studies suggest that ZFX may be a key regulator in cancer cells of the high transcriptional output from thousands of CpG island promoters (Rhie et al 2018).

(a) Bieda M, Xu S, Singer M, Green R, **Farnham PJ**. Unbiased location analysis of E2F1 binding sites suggests a widespread role for E2F1 in the human genome. **Genome Research** 16: 595-605, 2006. PMC145704. This manuscript documents that E2F binding sites are dictated by proximity to RNAPII binding sites; given a "must read" ranking at Faculty of 1000: F1000.com /1029798/.

(b) Eberhardy SR, **Farnham PJ**. Myc recruits P-TEFb to mediate the final step in the transcriptional activation of the cad promoter. **Journal of Biological Chemistry** 277: 40156-40162, 2002. PMID:11673469. The first demonstration that the MYC oncogene regulates transcription by stimulating a paused RNA polymerase II to begin elongation.

(c) Tak YG, Hung Y, Yao L, Grimmer MR, Do A, Bhakta M, O'Geen H, Segal DJ, **Farnham PJ**. Effects on the transcriptome upon deletion of a distal element cannot be predicted by the size of the H3K27Ac peak in human cells. **Nucleic Acids Research** 2016 Jan 6. pii: gkv1530. PMID:26743005. This manuscript uses CRISPR/Cas9 technology to delete enhancers from the human genome, followed by analysis of the epigenome, transcriptome, and cellular phenotype of the deleted cells.

(d) Rhie SK, Yao L, Luo Z, Witt H, Schreiner S, Guo Y, Perez AA, **Farnham PJ**. ZFX acts as a transcriptional activator in multiple types of human tumors by binding downstream of transcription start sites at the majority

of CpG island promoters. **Genome Research** 28: 310-320, 2018. PMID:29429977. This manuscript describes a new class of transcription factors that bind to CpG island promoters between the transcription start site and the first downstream nucleosome, suggesting that the ZFX family may play a critical role in promoter architecture and in regulating the cancer transcriptome.

3. Mechanisms that establish the epigenome: In addition to my contributions as a member of the Roadmap Epigenome Mapping Consortium, my laboratory has independently studied the mechanisms by which the epigenome is established and regulated. In 2004 we used ChIP-chip to identify the first gene silenced by deposition of H3K27me3 by the PRC2 complex (see Kirmizis et al, 2004, listed above) and then performed a comprehensive analysis to demonstrate cell type-specific binding of Suz12 (a component of PRC2), providing the first evidence that PRC2 complexes can spread through large regions of the genome (Squazzo et al. 2006). We have also studied the KAP1/SETDB1 epigenetic repression complex which deposits H3K9me3. We were the first to demonstrate the zinc finger genes were coated with H3K9me3 (O'Geen et al. 2007) and went on to characterize the ZNF274/KAP/SETDB1 complex that establishes this mark (Frietze et al. 2010; Iyengar et al. 2011).

(a) Squazzo SL, Komashko VM, O'Geen H, Krig S, Jin VX, Jang S-W, Green R, Margueron R, Reinberg D, **Farnham PJ**. Suz12 silences large regions of the genome in a cell type-specific manner. **Genome Research** 16:890-900, 2006. PMC1484456. This manuscript provides the first evidence that PRC2 complexes can spread through large regions of mammalian genomes.

(b) O'Geen H, Squazzo SL, Iyengar S, Blahnik K, Rinn JL, Chang HY, Green R, **Farnham PJ**. Genome-wide analysis of KAP1 binding suggests an auto-regulation of KRAB-ZNFs. **PLOS Genetics** 3, e89 doi:10.1371/journal.pgen.0030089, 2007. PMC1885280. A genome-scale ChIP-chip comparison revealed that zinc finger genes are bound by H3K9me3 and homeobox genes are bound by H3K27me3; given a "Recommended" ranking at Faculty of 1000: F1000.com /1087864/.

(c) Frietze S, O'Geen H, Blahnik KR, Jin VX, **Farnham PJ**. ZNF274 recruits the histone methyl-transferase SETDB1 to the human genome. **PLOS One** 5:e15082, 2010. PMID: 2117033. PMC2999557. This manuscript identifies the first KRAB-ZNF shown to recruit the SETDB1 epigenetic complex to specific sites in the human genome.

(d) Iyengar S, Ivanov AV, Jin VX, Rauscher FJ III, **Farnham PJ**. Functional analysis of KAP1 genomic recruitment. **Molecular and Cellular Biology** 31:833-1847, 2011. PMID: 21343339. This manuscript provides in vivo support for the model that KRAB-ZNFs recruit KAP1 to the genome via the N terminal RBCC domain.

4. Epigenomic regulation of cancer. In addition to studying the mechanisms that establish the epigenome, I have also investigated the influence of epigenomic regulation on cancer cell biology. My lab has studied the effects of DNA methylation and histone acetylation of the cancer transcriptome. We have shown that inhibition by an epigenetic inhibitor of DNA methylation can reorganize the pattern of repressive histone marks and have severe consequences on gene expression and that loss of DNA methylation due to mutation of DNA methyltransferases can cause a remodeling of H3K27Ac patterns and the acquisition of new enhancers (Blattler et al. 2014). We have used DNA methylation and expression data from TCGA to define transcription networks and identify putative target genes of enhancers that are hypomethylated in human cancers (Rhie et al. 2016). We have recently begun characterizing 3-dimensional epigenomic regulation of cancer cells by incorporating genome-wide chromatin contact information into studies of cancer risk SNPs (Luo et al. 2017; Guo et al. 2018).

(a) Blattler A, Yao L, Witt H, Guo Y, Nicolet CM, Berman BP, **Farnham PJ**. Global loss of DNA methylation uncovers intronic enhancers in genes showing expression changes. **Genome Biology** 15:469, 2014. PMID:25239471. This manuscript shows that DNA methylation plays an important role in the regulation of distal elements, identifying intronic enhancers activated by loss of DNA methylation.

(c) Rhie SK, Guo Y, Yao L, Shen H, Coetzee GA, Laird PW, **Farnham PJ**. Identification of activated enhancers and linked transcription factors in breast, prostate, and kidney tumors by tracing enhancer networks using epigenetic traits. **Epigenetics and Chromatin** 9:50. eCollection 2016. PMID:27833659. This manuscript identifies tumor-specific enhancers and critical TFs using a novel bioinformatic method called TENET.

(d) Luo Z, Rhie SK, Lay FD, **Farnham PJ**. A Prostate Cancer Risk Element Functions as a Repressive Loop that Regulates HOXA13. **Cell Reports** 21:1411-1417, 2017. PMID:29117547. This manuscript demonstrates that, upon CRISPR-mediated deletion of a regulatory region associated with prostate cancer, the HOXA13 gene located ~900 kb away is upregulated.

Guo Y, Perez A, Hazelett DJ, Coetzee GA, Rhie SK, **Farnham PJ**. CRISPR-mediated deletion of prostate cancer risk-associated CTCF loop anchors identifies repressive chromatin loops. **Genome Biology**, In press 2018. This manuscript identifies GWAS risk loci involved in long-range loops that function to repress gene expression within chromatin loops. Our studies provide new insights into the genetic susceptibility to prostate cancer.

Complete list of published work in PubMED as of September 2018.
https://www.ncbi.nlm.nih.gov/sites/myncbi/peggy.farnham.1/bibliography/40433784/public/?sort=date&direction=ascending

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D.

ONGOING RESEARCH SUPPORT

NIH R01CA136924 (Farnham, Coetzee, Lu [Multi-PI]) 03/15-01/20
Prostate Cancer Risk Enhancers. The goals of this project are to identify the target genes of enhancers that are associated with increased risk for prostate cancer.

NIH R21HG009742 (PI: Farnham; Segal/UC Davis: co-investigator) 09/17-06/19
Development of a novel promoter tagging technology to identify enhancer targets.
The goals of this project are to develop methods to identify promoter-enhancer interactions in cancer cells.

NIH 2 P30 CA014089 (PI: Farnham) 12/15-12/20
USC Norris Comprehensive Cancer Center Core Grant.
The goal of this project is to support the USC Cancer Center.
Role: Interim Director

COMPLETED RESEARCH SUPPORT (within the last 5 years)

NIH/NCI R01 CA045240 (Farnham: PI) 04/87-05/12
Transcriptional Regulation of Growth-Related Genes. The aims were to study transcriptional regulation mediated by E2F/Rb complexes and by epigenetic regulatory complexes.

NIH/NHGRI U54HG004558 (Snyder: PI; Farnham: co-investigator) 09/07-08/12
Production Center for Global Mapping of Regulatory Elements. The goals were to establish a production facility for mapping genomic binding sites of hundreds of transcription factors.

NIH U01 ES017154 (PI: Costello; Farnham co-investigator) 09/08-08/13
Integrated epigenetic maps of human embryonic and adult cells. The goals were to map epigenomes of select human cells with significant relevance to complex human disease

NIH/NHGRI R21 HG006761 (Farnham: PI) 04/12-03/15
Development of a nuclease-mediated technology to validate chromatin hubs. The goals of this project were to develop methods to delete enhancer regions in the human genome.

NIH/NHGRI U54HG006996 (PI: Snyder; Farnham: co-investigator) 09/12-07/17
Production Center for Global Mapping of Regulatory Elements. The goals of this project were to complete the mapping of regulatory elements in the human genome.

NIH R21CA204563 (PI: Segal/UC Davis; Farnham: co-investigator) 07/16-06/18
Crisper-based epigenetic modifiers. The goals of this project are to engineer a toolbox of highly specific and targetable dCas9-based modifiers that can manipulate the epigenome in a predictable manner.

NIH U01MH103346 (Farnham, Knowles [Multi-PI]) 04/14-05/18
The USC PsychENCODE Consortium. The goals of this project are to map the epigenome, transcriptome, and nucleosome patterning in control and schizophrenic patients**.**