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 Biology

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. More recently, 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 two aspects of cancer research, characterization of the genome-wide effects of epigenetic chemotherapeutic inhibitors and molecular characterization of cancer-associated enhancers. We have expertise in the use of genomic nucleases and artificial transcription factors based on zinc finger, TALEN, and CRISPR platforms.

I am a member of the ENCODE Consortium, whose goal is to map all the functional elements in the human genome, mainly focusing on cancer cell lines. I was also a member of the NIH Roadmap Epigenome Mapping Consortium, which just recently published epigenome for ~100 normal cell types. I have recently been funded as part of the PsychENCODE project, which is seeking to expand the ENCODE assays to the analysis of pyschiatric disorders. 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 162 of my publications and reports a current h-index of 64; over the last 10 years my publications have been cited an average of 884 times/year with 2200 citations in 2014.

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) Farnham, PJ. Insights from genomic profiling of transcription factors. Nature Reviews Genetics 10:605-616, 2009. PMID: 19668247. PMC2846386
(c) THE ENCODE CONSORTIUM. An Integrated Encyclopedia of DNA Elements in the Human Genome. Nature 489:57-74, 2012. PMID:22955616.
(d) Roadmap Epigenome Mapping Consortium. Integrative analysis of 111 reference human epigenomes. Nature, 518:317-330, 2015. PMID: 25693563

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, USC/Norris Cancer Center, USC, Los Angeles, CA
2013-2015: Associate Dean of Graduate Affairs, Keck School of Medicine USC, Los Angeles, CA
2015-present: Chair, Department of Biochemistry and Molecular Biology, 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-present: Member of NHGRI-sponsored ENCODE Consortium
2008-present: Member of NIH Roadmap Reference Epigenome Mapping Centers
2013-present: Member of NIH-sponsored PyschENCODE Consortium

Honors

NIH Predoctoral Fellow, 1978-1982.
Damon Runyon-Walter Winchell Postdoctoral Fellow, 1982-1983.
NIH Postdoctoral Fellow, 1983-1986.
Outstanding Mentor in the U.W. Medical School, 1997, 1998
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 high density oligonucleotide arrays for human ChIP-chip studies (**Kirmizis et al. 2004**). My lab then moved into ChIP-seq and developed protocols and programs for this new technology. We have recently 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 development is the use of CRISPR/Cas9 genomic nucleases to delete enhancers from the human genome (**Yao et al. 2014**).

(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 & Dev. 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) Kirmizis A., Bartley SM, Kuzmichev A, Margueron R, Reinberg R, Green R, **Farnham PJ**. Silencing of human polycomb target genes is associated with methylation of histone H3 lysine 27. Genes & Dev. 18:1592-1605, 2004. PMC443521. **This manuscript describes the first use of NimbleGen arrays for ChIP-chip**.

(c) 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 Res. 42:10856-10868, 2014. PMID:25122745. **This manuscript provides the first genome-wide ChIP-seq analysis of an artificial zinc finger epigenetic regulator.**

(d) 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.**

2. Insights into transcriptional regulation: My work has focused on understanding transcriptional regulation mediated by E2F1 and MYC. I have published ~50 corresponding author research articles (not including reviews or book chapters) 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 using ChIP-chip, 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 (**Cao et al, 2011**). 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 recently used CRISPR/Cas9 genomic nucleases to study transcriptional regulation in vivo, deleting an enhancer that regulates MYC, resulting in downregulation of hundreds of MYC target genes (**Tak et al. in press, 2016**).

(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 Res. 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) Cao AR, Rabinovich R, Xu, M., Xu X, Jin VX, Farnham PJ. Genome-wide analysis of transcription factor E2F1 mutant proteins reveals that N- and C-terminal protein interaction domains do not participate in targeting E2F1 to the human genome. J. Biol. Chem. 286:11985-96, 2011. PMID: 21310950. PMC3069401. **This manuscript describes a novel ChIP-seq analysis of mutant proteins to show that E2F1 genomic binding requires the DNA binding domain, even when bound to regions lacking an E2F motif.**

(c) Eberhardy SR, Farnham PJ. Myc recruits P-TEFb to mediate the final step in the transcriptional activation of the cad promoter. J. Biol. Chem., 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.**

(d) 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. In Press, 2016. **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.**

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. We began our studies in 2004, using 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 Res. 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 (**Komashko and Farnham, 2010**) 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 also studied epigenetic inhibitors of histone acetylation, showing that inhibiting the CBP and p300 histone acetyltransferases can have cancer type-specific effects (**Gaddis et al. 2015**). Finally, we have developed an R Bioconductor package which uses DNA methylation and expression data from TCGA to define transcription networks and identify putative target genes of enhancers that are hypomethylated in human cancers (**Yao et a. 2015**).

(a) Komashko VM and **Farnham PJ**. 5-azacytidine treatment reorganizes genomic histone modification patterns. Epigenetics 5: 229-240, 2010. PMID: 20305384. **This manuscript demonstrates that treatment of cells with a DNA methylation inhibitor causes large changes in histone modifications; in particular, H3K9me3 is lost over zinc finger genes.**

(b) 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 many new intronic enhancers that are activated by loss of DNA methylation.**

(c) Gaddis M, Gerrard D, Frietze S, Farnham PJ. Altering cancer transcriptomes using epigenomic inhibitors. Epigenomics and Chromatin 8:9, 2015. PMID: 26191083. **This manuscript demonstrates that treatment with ICG-001 (a HAT inhibitor) affects the WNT pathway in colon cancer cells and the cholesterol biosynthesis pathway in pancreatic cancer cells.**

(d) Yao L, Shen H, Laird PW, Farnham PJ, Berman BP. Inferring regulatory element landscapes and transcription factor networks from cancer methylomes. Genome Biol. 16:105, 2015. PMID: 25994056. **This manuscript describes a bioinformatic program that uses DNA methylation and expression data from TCGA to define transcription networks and identify putative target genes of enhancers that are hypomethylated in human cancers.**

Complete list of published work in PubMED as of January 2016.

http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40433784/?sort=date&direction=descending