BIOGRAPHICAL SKETCH

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NAME: GILL, GRACE B

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

POSITION TITLE: Associate Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of California Berkeley, Berkeley, CA	BA	06/1983	Molecular Biology
Harvard University, Cambridge, MA	PhD	06/1989	Biochemistry
University of California, Berkeley, Berkeley, CA	Postdoctoral Fellow	08/1994	Mechanisms of Gene Regulation

A. Personal Statement

I am a recognized expert in the gene expression field, with a track record of research whose findings have been transformative to the approaches and understanding of molecular mechanisms of transcriptional activation and repression in eukaryotes. Studies from my laboratory established that post-translational modification by the small ubiquitin related modifier, SUMO, promotes association with co-repressors that alter the chromatin landscape. We identified many SUMO interacting co-repressors with chromatin modifying activities, including CoREST1, a co-factor for the histone lysine demethylase LSD1. We leveraged our studies of basic mechanisms of chromatin structure and gene expression to investigate the regulation of gene expression programs important for cell phenotype in both normal breast development and aggressive, basal-like, breast cancers. My laboratory has also advanced understanding of how post-translational modification of transcription factors contributes to complex programs of gene expression important for establishing and maintaining proper connections in the mammalian nervous system and how these pathways are disrupted in neuropsychiatric disorders such as bipolar disorder and Schizophrenia.

In addition to my research accomplishments, I have a record of active and successful training and mentoring of young scientists. I was the research advisor for 11 post-doctoral fellows, 3 PhD students, 2 Masters' students, and 7 Harvard undergraduates, of whom 5 did Honors Thesis research in my lab. All of the PhD students and postdoctoral fellows who trained with me have continued in biomedical research careers. I have served on 40 PhD thesis advisory committees (11 as Chair) and I have advised and mentored numerous postdoctoral fellows in other labs, either formally as part of the IRACDA program at Tufts, or informally, as fellows sought out my advice on research projects, presentations, and professional development. I held leadership positions in the graduate school at Tufts University School of Medicine and I implemented initiatives to improve graduate training for over 1200 PhD students in the life sciences at the Graduate School of Arts & Sciences at Harvard University. I am a Certified Facilitator of Entering Mentoring by Center for the Improvement of Mentored Experiences in Research (CIMER), based on positive reviews from faculty participants in the full-length, 9-10-hour, workshops that I co-facilitated. At the Knight Cancer Institute, I support professional development of junior faculty and coordinate across our many training programs. I am currently co-Director of the Cell, Developmental & Cancer Biology Summer Research Internship at the Knight Cancer Institute, a pipeline program to engage college students, many from underrepresented backgrounds, in biomedical research. I am delighted to bring my strong foundations in pre-clinical, basic science research and my dedication to equitable training to my role as co-Associate Program Director for the Experimental Therapeutics in Cancer Training Program.

B. Positions, Scientific Appointments, and Honors

Positions and Employment

2023-present	Co-Associate Director of Cancer Research Training, Knight Cancer Institute, Oregon Health & Science University, Portland, OR
2022-present	Associate Professor, Division of Oncological Sciences, Dept. of Cell, Developmental and Cancer Biology, Oregon Health & Science University, Portland, OR
2020-2021	Director, Academic Programs, Harvard University Graduate School of Arts & Sciences, Harvard University, Cambridge, MA
2017-2020	Director, Harvard Integrated Life Sciences, Harvard University Graduate School of Arts & Sciences, Harvard University, Cambridge, MA
2016-2017	Senior Scientific Editor, Cell Reports, Cell Press, Elsevier, Cambridge, MA
2013-2016	Associate Professor, Dept. of Developmental, Molecular and Chemical Biology, Tufts University School of Medicine, Boston, MA
2007-2013	Associate Professor, Dept. of Anatomy and Cellular Biology, Tufts University School of Medicine, Boston, MA
2003-2006	Associate Professor, Department of Pathology, Harvard Medical School, Boston, MA
2000-2001	Visiting Scientist, Cell and Molecular Cell, Cell Press, Cambridge, MA
1997-2000	Instructor, Eukaryotic Gene Expression Course, Cold Spring Harbor Laboratory, NY
1995-2000	Tutor, Biochemical Sciences, Harvard University
1994-2003	Assistant Professor, Department of Pathology, Harvard Medical School, Boston, MA
1989-1994	Postdoctoral Research Fellow with Dr. Robert Tjian, Department of Molecular and Cell Biology, University of California, Berkeley. Mechanism of Transcriptional Activation by Sp1
1983-1989	Graduate student Researcher, Dr. Mark Ptashne, Department of Biochemistry and Molecular Biology, Harvard University. The Transcriptional Activation Function of GAL4
1982-1983	Undergraduate Researcher, Dr. Stephen Beckendorf, Department of Molecular Biology, University of California, Berkeley. Regulation of Drosophila glue protein gene expression

Other Experience and Professional Memberships (selected)

2022	Certified Facilitator, Entering Mentoring, Center for the Improvement of Mentored Experiences in Research (CIMER)
2014 - 2015	Member, Program Planning Committee, American Society for Biochemistry and Molecular Biology 2015 Annual Meeting; Co-Theme Organizer, “RNA expression and post-transcriptional regulatory events”
2014	Ad Hoc Reviewer, Fellowships: Neurodevelopment, Synaptic Plasticity and Neurodegeneration, ZRG1 F03A, National Institutes of Health
2013	Ad Hoc Reviewer, Special Emphasis Panel ZGM1, National Institutes of Health
2012 – 2016	Member, Program Steering Committee U54 UMass Boston-Dana Farber/Harvard Cancer Center Partnership
2009-2015	Member, Editorial Board, Transcription
2008- 2011, 2014-2016	Committee on Programs and Faculty, Sackler School of Graduate Biomedical Sciences, Tufts University School of Medicine; 2 years as **Chair**
2006-2010	Permanent Member, Molecular Genetics C Study Section, National Institutes of Health
2004	Temporary Member, Biochemistry Study Section, National Institutes of Health
2001-2016	Member, Editorial Board, Molecular Cell

Honors

2002	Fellow, Hellman Family Faculty Fund at Harvard Medical School
1997	Basil O’Connor Starter Scholar Research Award, The March of Dimes
1996	New Investigator Award, The Jesse B. Cox Charitable Trust, The Medical Foundation
1992	Senior Fellow, American Cancer Society, California Division
1989	Fellow, Jane Coffin Childs Memorial Fund for Medical Research
1987	Certificate of Distinction in Teaching, Harvard University
1982	Phi Beta Kappa, University of California, Berkeley

C. Contributions to Science

SUMO-modification of transcription factors promotes association with co-repressors that have chromatin-modifying activity

Many transcription factors are post-translationally modified by the small ubiquitin related modifier, SUMO. We reported that transcription factor Sp3 is post-translationally modified by SUMO and, further, that SUMO modification is required for the repressor activity of Sp3 on reporter genes. As part of this work, we generated fusions of SUMO to Sp3 or to the Gal4 DNA binding domain and found that localization of SUMO to the promoter was sufficient to repress transcription. Our studies established the method of using SUMO fusions to analyze the impact of substrate SUMOylation and were the first to show that SUMO has an intrinsic repression function. Our findings supported the view that SUMO alters the activity of transcription factors such as Sp3 by promoting interactions with co-repressors that have SUMO interaction motifs (SIMs). We went on to identify many SUMO binding co-repressors with chromatin modifying activities. Our studies of CoREST1 revealed that non-covalent interaction of a novel type of SIM in CoREST1 with SUMO-2/3 is required for gene specific localization and repression by the LSD1/CoREST1/HDAC histone modifying complex.

a. Ross, S., Best, J.L., Zon, L., and **Gill, G.** SUMO-1 modification represses Sp3 transcriptional activation and modulates its subnuclear localization. Molecular Cell 2002; 10: 831-842.
b. Rosendorff, A., Sakakibara,S., Lu,S., Kieff,E., Xuan,Y., DiBacco, A., Shi, Y., Shi, Y., and **Gill, G.** NXP-2 association with SUMO-2 depends on lysines required for transcriptional repression. Proc. Nat. Acad. of Sciences, 2006; 103, 5308-5313. PMCID: PMC1459351
c. Di Bacco A., Ouyang, J., Lee, H.-S., Catic, A. Ploegh, H., and **Gill, G.** The SUMO-specific protease SENP5 is required for cell division. Mol. Cell Biol. 2006; 26, 4489-4498. PMCID: PMC1489136
d. Ouyang, J., Shi, Y., Valin, A., Xuan, Y., and **Gill, G.** Direct binding of CoREST1 to SUMO-2/3 contributes to gene-specific repression by the LSD1/CoREST1/HDAC complex. Molecular Cell, 2009; 34, 145-154. PMCID: PMC2727917 **Recommended by Faculty of 1000 Biology**

The chromatin regulators LSD1 and CoREST1 regulate cell fate and tumorigenesis

The altered expression and/or activity of enzymes that post-translationally modify histones contributes to pathogenesis of many cancers. The first identified histone demethylase, LSD1, often functions in complex with a partner, CoREST1. CoREST1 is required for LSD1-mediated demethylase activity on nucleosomal substrates and also regulates recruitment to specific genes through protein-protein interactions with DNA binding proteins, and, as we have shown, via non-covalent interactions with SUMO-2. We helped describe a larger complex including the histone deacetylase SIRT1 together with LSD1/CoREST1 that regulates Notch target gene expression and cell fate. In collaboration with Charlotte Kuperwasser at Tufts University School of Medicine, we have examined the function of the LSD1/CoREST1 complex in normal and tumor-derived breast cells. Our studies support the hypothesis that LSD1/CoREST1 complex activity contributes to the development of aggressive breast cancer by altering chromatin structure and repressing transcription of specific genes associated with the luminal epithelial differentiation program. Unexpectedly, we have also found a role for CoREST1 in promoting growth of breast tumors via regulation of tumor/stroma interactions.

a. Mulligan, P., Yang, F., Di Stefano, L., Ji, J-Y., Ouyang, J., Nishikawa, J.L., Toiber, D., Kulkarni., M., Wang, Q., Najafi-Shoushtari, S.H., Mostoslavsky, R., Gygi, S.P., **Gill, G**., Dyson, N.J., Näär, A.M. A SIRT1-LSD1 Co-repressor Complex Regulates Notch Target Gene Expression and Development. Molecular Cell, 2011; 42, 689-699. PMCID:PMC3119599
b. Phillips,S., Prat,A., Sedic,M., Mazumdar,S., Shirley,S.H., Perou, C. **Gill, G.**, Gupta, P.B. Kuperwasser,C. Cell-state transitions regulated by Slug are critical for tissue regeneration and tumor initiation. Stem Cell Reports, 2014; 2(5), 633–647. PMCID: PMC4050485
c. Mazumdar, S., Arendt, L., Phillips, S., Sedic, M., Kuperwasser, C. and **Gill, G.**, CoREST1 promotes tumor formation and tumor stroma interactions in a mouse model of breast cancer. PLOS One, 2015;(10)3. PMCID: PMC4368644

Transcription factor Sp4 controls dendrite patterning and is actively regulated by Store-operated Ca^{2+} Entry (SOCE) in neurons

The pattern of dendrites and dendrite spines contributes to how a neuron integrates inputs. Sp1, Sp3 and Sp4 are highly related transcription factors. In contrast to Sp1 and Sp3, which are ubiquitously expressed, Sp4 levels are highest in the central nervous system and the brain, although the functions of Sp4 in neurons were not known. We used an RNAi knockdown approach to discover that Sp4 plays a non-redundant role in regulating dendrite patterning in developing cerebellar granule neurons. We have identified several Sp4 target genes including Nwk2 (Fchsd1), an F-BAR domain protein that controls NMDA receptor 1 surface levels and dendrite patterning. We further reported that Sp4 is required for membrane depolarization-dependent dendrite patterning and Sp4 phosphorylation and activity are regulated downstream of NMDAR signaling. In addition to voltage gated channels (VGCCs) such as the NMDAR, neurons also express Stim1 and Orai proteins that mediate Store-operated Ca^{2+} Entry (SOCE), but the regulation and function of SOCE in neurons had not been described. We discovered that SOCE is active in neurons at resting membrane potential, under conditions when VGCCs are not active. Further, our studies show that Ca^{2+} signaling downstream of SOCE regulates Sp4 protein stability and levels. Our findings indicate that SOCE not only functions to replenish calcium stores but SOCE also actively signals to promote changes in transcription factor activity in neurons.

a. Ramos, B., Gaudilliere, B., Bonni, A., and **Gill, G.** The transcription factor Sp4 regulates dendritic patterning during cerebellar development. Proc. Nat. Acad. of Sciences, 2007; 104; 9882-9887. PMCID: PMC1887555
b. Saia, G., Lalonde, J., Ramos, B**., Gill, G**. Phosphorylation of the transcription factor Sp4 is reduced by NMDA receptor signaling. J. Neurochem, 2014*;*129(4):743-52. PMCID: PMC39999283.
c. Sun, X., Pinacho, R., Saia, G., Punko, D., Meana, J.J., Ramos, B., **Gill, G.** Transcription Factor Sp4 regulates expression of Nervous Wreck 2 to control NMDAR1 levels and dendrite patterning*.* Dev Neurobiol. 2014; 75(1):93-108. PMCID: PMC4261064
d. Lalonde, J., Saia, G., **Gill, G.** Store-operated Ca^{2+} Entry Regulates Transcription Factor Sp4 in Resting Neurons. Sci Signaling,2014; 7(328) ra 51. PMCID:PMC4445882 **Featured in a Perspective in Sci Signaling**

Sp4 protein levels and post-translational modification are altered in Bipolar Disorder and Schizophrenia

Genetic studies have revealed an association between variations at the Sp4 locus and both Bipolar Disorder and Schizophrenia in humans, but it was not known whether or how Sp4 was altered in patients. I have collaborated with Belen Ramos at the Fondacio Sant Joan de Deu in Spain to examine Sp4 mRNA and protein levels in post-mortem brain samples. Strikingly, we found reduced Sp4 protein, but not mRNA, in postmortem cerebellum of Bipolar Disorder and we observed a correlation with Sp4 protein levels and negative symptoms in cerebellum of Schizophrenia. Further, we analyzed Sp4 phosphorylated at S770 and observed a relative increase in Sp4pS770 in cerebellum of Bipolar Disorder and associated with negative symptoms in Schizophrenia. Negative symptoms are the most stable cluster of symptoms in chronic patients and the most resilient to current available therapies. Our pilot studies pioneered the use of negative symptom dimension for association studies of these symptoms with molecular features. We also observed reduced Sp4 protein and increased Sp4pS770 in lymphocytes from first-episode psychosis subjects, suggesting these features may appear at the onset of disease. Further, we reported that lithium, a mood stabilizer commonly used for treatment of Bipolar Disorder, regulates Sp4 levels and S770 phosphorylation. Taken together, these studies support the model that the mechanisms that regulate Sp4 levels and stability are altered in neuropsychiatric disease and in response to some therapeutics.

a. Pinacho, R., Villalmanzo, N., Lalonde, J., Haro, JM., Meana,J., **Gill, G***, and Ramos, B*. (*co-corresponding). The transcription factor Sp4 is reduced in postmortem cerebellum of bipolar disorder subjects: Control by depolarization and lithium. Bipolar Disorders, 2011, *13*, 474-485. PMCID: PMC3202296
b. Pinacho, R., Villalmanzo, N., Roca.M., Iniesta,R., Monje, A., Haro, JM., Meana,J., Ferrer, I., **Gill, G**, and Ramos, B. Analysis of SP transcription factors in the postmortem brain of chronic schizophrenia: a pilot study of relationship to negative systems. J. of Psychiatric Research, 2013; 47(7), 926-934.

c. Pinacho, R., Saia, G., Meana, J.J., Ramos, B. and **Gill, G.** Transcription factor SP4 phosphorylation is increased in the postmortem cerebellum of bipolar disorder and schizophrenia subjects. Eur. Neuropsychopharmacology, 2015; (10):1650-60.
d. Pinacho, R., Saia, G., Fuste, M., Meléndez-Pérez, I., Villalta-Gil,V., Haro, J.M., **Gill, G.** and Ramos, B. Phosphorylation of transcription factor specificity protein 4 is increased in peripheral blood mononuclear cells of first-episode psychosis: Regulation by lithium. PLOS One, 2015; 10(4): e0125115. doi:10.1371. PMCID:PMC4411105

Modularity and function of eukaryotic activation domains

I contributed to early work defining activation domains in eukaryotic transcription factors. As a graduate student in Mark Ptashne's lab, I showed that *in vivo* binding to the promoter by the DNA binding domain of Gal4 was not sufficient for transcriptional activation. Together with other studies, this helped establish the now well-accepted view that eukaryotic transcription factors have separable DNA binding and activation (or repression) domains. This fundamental insight influenced models of activation mechanisms and laid the foundation for development of yeast two-hybrid approaches for screening protein interaction libraries. I also characterized key features of acidic activation domains in yeast and described how overexpression of activation domains could inhibit transcription by competition, a phenomenon dubbed "squelching". As a postdoctoral fellow with Robert Tjian, I helped establish that some activators stimulate transcription via interactions with components of the TFIID complex composed of TATA binding protein, TBP, and TBP associated factors, TAFs.

a. Keegan, L., **Gill, G.** and Ptashne, M. Separation of DNA binding from the transcription activating function of a eukaryotic regulatory protein. Science 1986; 231:699-704.
b. **Gill, G.** and Ptashne, M. Mutants of GAL4 protein altered in an activation function. Cell 1987; 51:121-126.
c. **Gill,G.** and Ptashne,M. Negative effect of the transcriptional activator GAL4. Nature 1988; 334: 721-724.
d. **Gill, G.**, Pascal,E., Tseng,Z.H., and Tjian,R. A glutamine-rich hydrophobic patch in transcription factor Sp1 contacts the $dTAF_{II}110$ component of the Drosophila TFIID complex and mediates transcriptional activation. Proc. Nat. Acad. of Sciences 1994; 91:192-196.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/grace.gill.1/bibliograpahy/41056210/public/?sort=date&direction=ascending