BIOGRAPHICAL SKETCH

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NAME: **W. Lee Kraus**

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POSITION TITLE: Director, Cecil H. and Ida Green Center for Reproductive Biology Sciences

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	FIELD OF STUDY
Cornell University, Ithaca, NY	B.S.	05/1989	Animal Physiology
University of Illinois, Urbana-Champaign	M.S.	05/1991	Physiol./ Cell, Mol. Biol.
University of Illinois, Urbana-Champaign	Ph.D.	05/1994	Physiol./ Cell, Mol. Biol.
University of Illinois, Urbana-Champaign	Postdoc	12/1994	Molecular Biology
University of California, San Diego	Postdoc	01/1999	Biochem., Mol. Biology

A. Personal Statement

My expertise is in the biophysical, biochemical, molecular, and genomic analysis of chromatin structure and signal-regulated transcription, especially as it relates to cancer, endocrinology, inflammation, and metabolism. In my lab at Cornell University (1999-2010) and UT Southwestern (2010-present), I have been studying the molecular biology, biochemistry, and genomics of signal-regulated transcription, with a focus on estrogen, TNFα, and nuclear NAD^+ signaling, especially as it relates to the function of estrogen receptors, NF-κB, other transcription factors, and poly(ADP-ribose) polymerases (PARPs). Since 2005, my lab has been using advanced genomics and bioinformatics approaches, including ChIP-seq and GRO-seq, and I have been instrumental in establishing these methodologies and building the related infrastructure at UT Southwestern. I am a leader in the fields of molecular endocrinology, nuclear receptors, and PARPs. I have been an organizer for international meetings on these topics, and serve as an editor or editorial board member for a number of journals in these areas. I am the founding organizer of the Cold Spring Harbor Laboratory meeting on PARPs and I served as a guest editor for a special PARP focus issue for *Molecular Cell*, a leading molecular biology journal, published in 2016. I am also a founder and consultant for Ribon Therapeutics, Inc., a company in the PARP inhibitor space operating in Boston since 2015. I have a strong interest in clinical and translational research, especially as it pertains to cancer, reproductive abnormalities, inflammation-based pathologies, and metabolic diseases. The outstanding faculty, resources, and environment at UT Southwestern are allowing me to pursue these interests in a comprehensive, detailed, and forward-looking manner.

B. Positions and Honors

Positions and Employment:

5/94 to 12/94	Postdoctoral Research Associate, Department of Physiology and Biophysics, University of Illinois, Urbana-Champaign (with Dr. Benita Katzenellenbogen).
1/95 to 1/99	Postdoctoral Fellow, Department of Biology, University of California, San Diego (with Dr. Jim Kadonaga).
2/99 to 6/04	Assistant Professor, Department of Molecular Biology and Genetics. Cornell University, Ithaca, NY.
9/00 to 9/06	Assistant Professor, Department of Pharmacology, Weill Medical College of Cornell University, New York, NY.
7/02 to 8/04 & 7/08 to 8/13	Instructor, Summer Short Course on Eukaryotic Gene Expression, Cold Spring Harbor Laboratories, CSH, NY.
7/04 to 6/09	Associate Professor, Department of Molecular Biology and Genetics. Cornell University, Ithaca, NY.
10/06 to 8/09	Associate Professor, Department of Pharmacology, Weill Medical College of Cornell University, New York, NY.
7/09 to 7/10	Professor, Dept. of Molecular Biology and Genetics. Cornell University, Ithaca, NY.
9/09 to 7/10	Professor, Dept. of Pharmacology, Weill Medical College of Cornell University, New York, NY.

7/10 - present	Professor and Vice Chair for Basic Sciences, Department of Obstetrics and Gynecology, Professor of Pharmacology, UT Southwestern Medical Center, Dallas.
7/10 - present	Director, Cecil H. and Ida Green Center for Reproductive Biology Sciences, UT Southwestern Medical Center, Dallas.
4/15 - present	Founder and Consultant, Ribon Therapeutics, Inc., Boston, MA.
4/17 - present	Guest Professor, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China.

Other Experience and Professional Memberships:

1994 to present	Member, American Association for the Advancement of Science.
1996 to present	Member, The Endocrine Society (Membership Committee, 2003 to 2006; Annual Meeting Steering Committee, 2006 to 2009).
Since 1999	Ad hoc reviewer for *Cancer Cell, Cell, Cell Metabolism, EMBO J.*, *EMBO Reports, Genes and Development, Journal of Biological Chemistry, Molecular Cell, Nature, Nature Cell Biology, Nature Communications, Proc. Natl. Acad. Sci. USA., Science*.
2000 to present	Member, The American Society for Microbiology.
2001 to 2010	Abstract reviewer, The Endocrine Society Annual Meeting.
2006 to 2008	Co-organizer, 2008 Keystone Meeting on Nuclear Receptors (NRs): Steroid Sisters.
2007 to 2009	Editorial Board, *Molecular Endocrinology.*
2007 to 2010	Standing Member, NIH Molecular and Cellular Endocrinology (MCE) Study Section.
2008 to 2019	Editorial Board, *Molecular and Cellular Biology.*
2008 to 2010	Lead organizer, 2010 Keystone Meeting on NRs: Signaling, Gene Reg. & Cancer.
2010 to present	Editorial Board, *Transcription.*
2011 to present	Member, The Society for the Study of Reproduction.
2011 to 2015	Editorial Board, *Trends in Endocrinology and Metabolism.*
2013 to 2018	Senior Editor, *Molecular Cancer Research*
2013 to 2017	Editor, *Molecular Endocrinology* (and *Endocrinology*)
2014 to present	Founding organizer, CSH Laboratory meeting on PARPs and ADP-ribosylation.
2018 to 2019	Co-organizer, 2019 FASEB meeting on NAD^+ Metabolism and Signaling.
2018 to 2019	Basic Science Chair, The Endocrine Society, 2019 Annual Meeting.

Honors:

1995 to 1998	NIH Postdoctoral Fellowship in Molecular Biology.
1998	American Cancer Society, California Division Postdoctoral Fellowship.
1998 to 2002	Burroughs Wellcome Fund Career Award in the Biomedical Sciences.
2004	Cornell University CALS Young Faculty Teaching Excellence Award.
2006	Univ. of Illinois, Dept. of Mol. & Integrative Physiology Distinguished Alumni Award.
2007	Endocrine Society's Richard E. Weitzman Memorial Award for research excellence.
2008	Cornell University CALS Excellence in Undergraduate Research Mentoring Award.
2010 to present	Cecil H. and Ida Green Distinguished Chair in Reproductive Biology Sciences, UT Southwestern Medical Center, Dallas.
2014	Endocrine Society's Ernst Oppenheimer Award for research excellence.

C. Contributions to Science

My research as a student, postdoc, and PI over the past 25 years has contributed to our understanding of the mechanisms of signal-regulated gene transcription, especially related to estrogen and nuclear NAD^+ signaling. My studies, which have been at the forefront of research on chromatin, transcription regulation, nuclear signaling pathways, and genomics, have fundamentally changed our understanding of how signal-regulated transcription factors, coregulator complexes, and histone- and chromatin-modifying enzymes collaborate to modulate chromatin structure and gene expression. This work has provided new insights into the molecular mechanisms that underlie gene regulation in a variety of biological systems, from reproduction and metabolism to cancer and inflammation. Publications list: http://www.ncbi.nlm.nih.gov/pubmed/?term=kraus+wl

1) *Nuclear Receptors, Chromatin, and Gene Regulation*

Although the contribution of chromatin to gene regulation was recognized and studied in the 1970s and 1980s, it wasn't until 1996 that Allis, Berger, and colleagues linked enzymatic modification of histones by coregulators to gene regulation. This started a revolution in the field of gene regulation and necessitated new methods to explore transcriptional regulation by physiologically relevant transcription factors and coregulators. As a postdoc with Jim Kadonaga ay UC San Diego, I was the first to develop an in vitro chromatin assembly

and transcription system that precisely and faithfully recapitulates the known physiological specificity of transcription regulation by steroid hormones acting through their cognate nuclear receptors. This work moved nuclear receptor-regulated transcription into a defined molecular system where it could, for the first time, be studied using powerful biochemical analyses. Collectively, these and subsequent studies in my own lab showed that chromatin, rather than being an inert substrate for transcription, actually plays a key role in determining signal-dependent transcriptional outcomes, ligand-dependent responses, and coactivator function.

Acevedo M. L., Lee K. C., Stender J. D., Katzenellenbogen B. S., **Kraus W. L.** (2004) Selective recognition of distinct classes of coactivators by a ligand-inducible activation domain. *Molecular Cell* 13:725-738. PMID: 15023342

Danko C. G., Hah N., Luo X., Martins A., Siepel A., **Kraus W. L.** (2013) Signaling pathways differentially affect RNA polymerase II initiation, pausing, and elongation rate in cells. *Molecular Cell* 50:212-222. PMCID: PMC3640649

Franco H.L., Nagari A., **Kraus W.L.** (2015) TNFα signaling exposes latent estrogen receptor binding sites to alter the breast cancer cell transcriptome. *Molecular Cell.* 58:21-34. PMCID: PMC25752574

Murakami S., Nagari A., **Kraus W.L.** (2017) Dynamic assembly and activation of estrogen receptor α enhancers through coregulator switching. *Genes Dev.* 31:1535-1548. PMID: 28887413

2) *Signal-Regulated Transcriptomes and Non-Coding RNAs*

The past decade has seen an incredible growth of genomic approaches to query gene regulation and the nature of the transcriptome on a global scale. My lab has leveraged new genomic methodologies, including global run-on sequencing (GRO-seq), to explore the signal-regulated transcription in multiple cells types, including breast cancers. We have also annotated new non-coding RNAs, including long non-coding RNAs (lncRNAs), antisense RNAs, and enhancer RNAs, and have begun to explore their functions. Furthermore, we have used genomic assays to examine the molecular mechanisms that drive signal-regulated transcriptional responses. These studies have characterized: (1) the robust and rapid changes that occur across the genome in response to estrogen and TNFα, (2) the assembly of functional transcriptional enhancers at transcription factor binding sites, and (3) the expression of thousands of previously unannotated noncoding RNA transcripts, significantly altering our view of signal-regulated transcriptional responses.

Hah N., Danko C. G., Core L., Waterfall J. J., Siepel A., Lis J. T., **Kraus W. L.** (2011) A rapid, extensive, and transient transcriptional response to estrogen signaling in breast cancer cells. *Cell* 145:622-634. PMCID: PMC3099127

Hah N., Murakami S., Nagari A., Danko C.G., **Kraus W. L.** (2013) Enhancer transcripts mark active estrogen receptor binding sites. *Genome Research* 23:1210-1223. PMCID: PMC3730096

Luo X., Chae M., Krishnakumar R., Danko C. G., Kraus W.L. (2014) Dynamic reorganization of the AC16 cardiomyocyte transcriptome in response to TNFα signaling revealed by integrated genomic analyses. *BMC Genomics*. 15:155. PMCID: PMC3945043

Sun M., Gadad S.S., **Kraus W.L.** (2015) Discovery, annotation, and functional analysis of long noncoding RNAs controlling cell cycle gene expression and growth in breast cancer cells. *Molecular Cell.* 59:698-711. PMCID: PMC4546522

3) *PARPs, NAD^+, and ADP-ribosylation: Links to Chromatin Structure and Gene Regulation*

Studies of poly(ADP-ribosyl)ation by nuclear poly(ADP-ribose) polymerases (PARPs) enzymes was largely focused on their roles in DNA damage detection and repair in the 1960s through 1990s. In the early 2000s, my lab was one of a small number that began to link PARP-1, and abundant nuclear PARP, to the regulation of chromatin structure and gene regulation. Using a range of biophysical, biochemical, and molecular approaches, my lab found that PARP-1 plays keys roles in the modulation of chromatin structure and gene expression in response to extracellular signals, such as those mediated by estrogens and TNFα. In addition, my lab has taken the lead in trying to understand how the synthesis of nuclear NAD^+, the substrate for PARP-1, by the nuclear NAD^+ synthase NMNAT-1 controls the gene regulatory functions of PARP-1 and downstream biological outcomes. These studies have linked cellular metabolic state, especially in the nucleus, to signal-regulated transcriptional outcomes.

Kim M. Y., Mauro S. A., Gévry N., Lis J. T., **Kraus W. L.** (2004) Modulation of chromatin structure and transcription by nucleosome-binding properties of PARP-1. *Cell* 119:803-814. PMID: 15607977

Krishnakumar R., **Kraus W. L.** (2010) PARP-1 Regulates chromatin structure and transcription through a KDM5B-dependent Pathway. *Molecular Cell* 39:736-749. PMCID: PMC2939044

Luo, X., Ryu K.W., Kim D.-K., Nandu T., Medina C.J., Gupte R., Gibson B.A., Soccio R.E., Yu Y., Gupta R., **Kraus W.L.** (2017) PARP-1 controls the adipogenic transcription program by PARylating C/EPBβ and modulating its transcriptional activity. *Molecular Cell* 65:260-271. PMID: 28107648

Ryu K.W., Nandu T., Kim J., Challa S., DeBerardinis R.J., **Kraus W.L.** (2018) Metabolic regulation of transcription through compartmentalized NAD^+ biosynthesis. *Science* 360:eaan570 and p. 618. PMID: 29748257.

4) *The 'Omics' of PARPs, ADP-ribosylation, and Related Factors*

'Omics' approaches, such as genomics and proteomics, have revolutionized the study if complex biological systems. The application of these methodologies to PARPs, ADP-ribosylation, and related factors, however, has lagged behind other areas of biology. My lab has been instrumental in bringing omics to the PARP field. We have used genomic methodologies, such as ChIP-seq and GRO-seq, to understand where nuclear PARPs localize across the genome and how they regulate gene expression. In addition, we have developed Click-ChIP-seq, the only method available to identify PARP-specific ADP-ribosylation events across the genome. We have also developed and used the most recent mass spectrometry-based proteomics approaches to identify the ADP-ribosylated proteome. This includes the development of an analog-sensitive PARP approach with clickable NAD^+ analogs PARP-specific ADP-ribosylation events proteome-wide.

Krishnakumar R., Gamble M. J., Frizzell K. M., Berrocal J. G., Kininis M., and **Kraus W. L.** (2008) Reciprocal binding of PARP-1 and histone H1 at promoters specifies transcriptional outcomes. *Science* 319:819-821. PMID: 18258916

Gamble M. J., Frizzell K. M., Krishnakumar R., **Kraus W. L.** (2010) The histone variant macroH2A1 marks repressed autosomal chromatin, but protects target genes from silencing. *Genes Dev.* 24:21-32. PMCID: PMC2802188

Gibson, B.A., Zhang, Y., Jiang, H., Hussey, K.M., Shrimp, J.H., Lin, H., Schwede, F., Yu, Y., and **Kraus, W.L.** (2016) Chemical genetic discovery of PARP targets reveals a role for PARP-1 in transcription elongation. *Science* 353:45-50. PMID: 27256882

Liu, Z., **Kraus W.L.** (2017) Catalytic-independent functions of PARP-1 determine Sox2 pioneer activity at intractable genomic loci. *Molecular Cell* 65:589-603. PMID: 28212747

5) *Applying Genomics, Bioinformatics, and Computational Biology to the Study of Gene Regulation*

To support the research described in 1 through 4 above, my lab has developed and/or applied a wide variety of genomic tools, including novel computational pipelines designed to integrate, analyze, and visualize data from a wide variety of genomic (and proteomic) platforms. These include groHMM, a hidden Markov model-based algorithm for predicting primary transcription units based on GRO-seq data. We have used groHMM, which we deposited as an R-based package in Bioconductor for the community to use freely, to annotated thousands of previously unannotated noncoding RNA transcripts of unknown function. In addition to generating useful tools, our studies have helped to elucidate new facets of the genome and transcriptome.

Danko C.G., Chae M., Martins A., **Kraus W.L.** (2014) groHMM: GRO-seq Analysis Pipeline. R package version 1.0.0. *Bioconductor*. (Software) www.bioconductor.org/packages/release/bioc/html/groHMM.html

Danko C.K., Hyland S.L., Core L.J., Martins A.L., Waters C.T., Lee H.W., Cheung V.G., **Kraus W.L.**, Lis J.T., Siepel A. (2015) Accurate identification of active transcriptional regulatory elements from global run-on and sequencing data. *Nature Methods*. 12:433-438. PMCID: PMC4507281

Chae M., Danko C.G., **Kraus W.L.** (2015) groHMM: A computational tool for identifying unannotated and cell type-specific transcription units from global run-on sequencing data. *BMC Bioinformatics* 16:222. PMCID: PMC4502638

Franco H.L., Nagari A., Malladi V., Li W., Xi Y., Richardson D., Allton K.L., Tanaka K., Li J., Murakami S., Keyomarsi K., Bedford M.T., Shi X., Li W., Barton M.C., Dent S.Y.R., **Kraus W.L.** (2018) Enhancer transcription reveals subtype-specific gene expression programs controlling breast cancer pathogenesis. *Genome Research* 28:159-170. PMID: 29273624

See also: Many of the papers listed in 1 through 4, above.

D. Research Support

Ongoing Research Support

R01 DK058110-17 - Kraus (PI) Period: 9/19/16 through 7/31/21 (5 years)
NIH/NIDDK

"Activity of Nuclear Receptor Coregulators with Chromatin"
Goal: To examine how the biochemical activities of nuclear receptor coregulators regulate the ligand-dependent transcriptional activity of estrogen receptors.

R01 DK069710-13 - Kraus (PI) Period: 6/1/13 through 5/31/17 (4 years)
NIH/NIDDK (under No Cost Extension; renewed awaiting NoA)
"The Role of PARP-1 in Hormone-Regulated Transcription"
Goal: To examine how the chromatin-regulating activities of poly(ADP-ribose) polymerase-1 (PARP-1) modulate ligand-dependent transcription by nuclear receptors.

RP160318/RP130607R1-01 - Kraus (PI) Period: 3/1/2016 - 2/28/2019 (3 years)
CPRIT
"Role of Long Non-Coding RNAs in Breast Cancers: Identification, Characterization, and Determination of Molecular Functions"
Goal: To determine the role of lncRNAs in breast cancer cell biology and their potential as therapeutic targets for controlling the growth and proliferation of breast cancer cells.

RP160319-01 - Kraus (PI) Period: 3/1/2016 - 2/28/2019 (3 years)
CPRIT
"Role of PARP-1 in Estrogen Receptor Enhancer Function and Gene Regulation Outcomes in Breast Cancers"
Goal: To determine the molecular mechanisms by which PARP-1 regulates ERα enhancer function.

P01 HD087150-01A1 - Mendelson (PD) 12/15/2016 - 11/30/2021 (5 years)
NIH/NICHD
"Molecular and Genomic Mechanisms in the Biology of Pregnancy and Parturition"
Kraus Roles:
• PI Project 2: "Estrogen Signaling and Estrogen Receptor Alpha Acetylation in the Pregnant Myometrium"
• PI Core 1: "Genomics and Computational Core"
Goals:
• Project 2: To determine the molecular mechanisms by which ERα acetylation controls ERα-dependent gene regulation in the myometrium.
• Core 1: To establish a Genomics and Computational Core (GCC) that will serve the four research projects.

Completed Research Support *(selection from the past three years)*

RP130607-03 - Kraus (PI) Period: 06/01/2013 through 11/30/2016 (3 years)
CPRIT
"Role of Long Non-Coding RNAs in Breast Cancers: Identification, Characterization, and Determination of Molecular Functions"
Goal: To determine the role of lncRNAs in breast cancer cell biology and their potential as therapeutic targets for controlling the growth and proliferation of breast cancer cells.

RP110471-P1-05 - Dent (PD) Period: 7/1/11 - 11/30/16 (5 years)
CPRIT (University of Texas M.D. Anderson)
"LONESTAR Oncology Network for Epigenetics Therapy and Research"
Kraus Role: Co-PI of Project 1: "Linking the epigenome to breast cancer etiology"
Goal (Project 1): To define epigenetic states important in driving breast cancer formation by defining the epigenomes of intrinsic breast cancer subtypes.

R21 HD075228-02 - Mahendroo (PI) Period: 07/01/2013 - 06/30/2015 (2 years)
NIH/NICHD
"Defining Gene Expression Programs in Cervical Ripening: Roles for Non-Coding RNAs"
Kraus Role: Co-PI
Goal: To use genomic approaches to determine how microRNAs control the gene expression in the cervix.