BIOGRAPHICAL SKETCH

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NAME: HANSEN, ULLA M

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POSITION TITLE: 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)	END DATE MM/YYYY	FIELD OF STUDY
Oberlin College, Oberlin, Ohio	BA	05/1974	Chemistry
Harvard University, Cambridge, Massachusetts	PHD	01/1980	Biochemistry and Molecular Biology
Massachusetts Institute of Technology, Cambridge, Massachusetts	Postdoctoral Fellow	01/1983	Molecular Biology

A. Personal Statement

During my faculty research career, my laboratory has contributed to understanding aspects of transcriptional activation and repression in mammalian cells, transcriptional responses to signaling pathways (e.g. estrogen; growth factors), and the transcriptional regulation that controls progression through critical points of the cell cycle. Over the years I have been sole Principal Investigator on a number of awards from both NIH and private foundations (e.g. the American Cancer Society, March of Dimes) to fund these projects. One major and continuing focus of my laboratory is the ubiquitous transcription factor LSF, which we were first to identify biochemically, and amongst the first to both clone the LSF cDNA and define the overall LSF gene family throughout the animal kingdom. Most significantly, we spearheaded understanding LSF's roles in cell growth, cell cycle, and survival. We characterized multiple translational modifications of LSF in response to signaling pathways, and demonstrated regulation of G1/S progression, and more recently of mitotic progression, by LSF. Our findings consistently suggested a role for LSF in cancer, which was validated by our demonstration with collaborators that LSF is an oncogene for hepatocellular carcinoma. Through our ongoing collaboration with Scott Schaus (Boston University), we identified and characterized specific small molecule inhibitors of LSF that inhibit tumor growth in multiple mouse models of hepatocellular carcinoma, with no observable toxicity, which led to a portfolio of two awarded patents plus another provisional application. Due to the potential clinical implications for this devastating disease, the focus of our research became translational. In recent years I obtained several shorter-term translational awards to fund these efforts. Overall, I have demonstrated a record of success in driving cutting-edge research, building the most extensive knowledge base on the transcription factor LSF, and working with expert collaborators, including Scott Schaus with his synthetic organic and medicinal chemistry focus, and starting with a new approach of LSF functionality, Andrew Emili with his extensive expertise in protein-protein complexes and mass spectrometry, such that we continue to uncover novel regulatory mechanisms regarding cell cycle and proliferation, and are poised to translate this basic knowledge into the clinics.

1. Hansen U, Schaus S, Grant T, Bishop J, Kavouris J, Christadore L, inventors. Trustees of Boston University, assignee. Inhibitors of Late SV40 Factor (LSF) as cancer chemotherapeutics. USA 9,815,845. 2017 November 14.
2. Rajasekaran D, Siddiq A, Willoughby JL, Biagi JM, Christadore LM, Yunes SA, Gredler R, Jariwala N, Robertson CL, Akiel MA, Shen XN, Subler MA, Windle JJ, Schaus SE, Fisher PB, Hansen U, Sarkar D. Small molecule inhibitors of Late SV40 Factor (LSF) abrogate hepatocellular carcinoma (HCC): Evaluation using an endogenous HCC model. Oncotarget. 2015 Sep 22;6(28):26266-77. PubMed PMID: 26313006; PubMed Central PMCID: PMC4694900.
3. Grant TJ, Bishop JA, Christadore LM, Barot G, Chin HG, Woodson S, Kavouris J, Siddiq A, Gredler R, Shen XN, Sherman J, Meehan T, Fitzgerald K, Pradhan S, Briggs LA, Andrews WH, Sarkar D, Schaus

SE, Hansen U. Antiproliferative small-molecule inhibitors of transcription factor LSF reveal oncogene addiction to LSF in hepatocellular carcinoma. Proc Natl Acad Sci U S A. 2012 Mar 20;109(12):4503-8. PubMed PMID: 22396589; PubMed Central PMCID: PMC3311344.

4. Yoo BK, Emdad L, Gredler R, Fuller C, Dumur CI, Jones KH, Jackson-Cook C, Su ZZ, Chen D, Saxena UH, Hansen U, Fisher PB, Sarkar D. Transcription factor Late SV40 Factor (LSF) functions as an oncogene in hepatocellular carcinoma. Proc Natl Acad Sci U S A. 2010 May 4;107(18):8357-62. PubMed PMID: 20404171; PubMed Central PMCID: PMC2889542.

B. Positions and Honors

Positions and Employment

1983 - 1988	Assistant Professor of Pathology, Dana-Farber Cancer Institute (DFCI), Harvard Medical School (HMS), Boston, MA
1983 - 1991	Chief, Laboratory of Eukaryotic Transcription, DFCI, Boston, MA
1983 - 1997	Member, Committee on Virology, Harvard Medical School, Boston, MA
1988 - 1990	Assistant Professor of Microbiology and Molecular Genetics, DFCI, HMS, Boston, MA
1991 - 1997	Principal Investigator, Division of Molecular Genetics, DFCI, Boston, MA
1991 - 1997	Associate Professor of Microbiology and Molecular Genetics, DFCI, HMS, Boston, MA
1998 -	Faculty Member, Program in Bioinformatics, Boston University, Boston, MA
1998 -	Professor, Department of Biology, Boston University, Boston, MA
2004 - 2006	Visiting Professor, Department of Medicine, Tufts Medical School, Boston, MA
2008 -	Director, Graduate Program in Molecular Biology, Cell Biology, and Biochemistry, Boston University, Boston, MA
2016 -	Affiliated Faculty Member, BU-CMD (Center for Molecular Discovery)
2016 -	Member, BU-BMC Cancer Center, Boston University

Other Experience and Professional Memberships

1984 -	Grant reviewer, National Science Foundation
1990 - 1990	Ad Hoc Member, NIH Virology Study Section
1994 - 1994	Ad Hoc Reviewer, American Cancer Society Scientific Advisory Committee on Personnel
1996 - 1997	Ad Hoc Reviewer, American Cancer Society Scientific Advisory Committee on Genetic Mechanisms in Cancer
1996 - 2001	Grant reviewer, The Israel Science Foundation
1998 - 1999	Reviewer, American Cancer Society Scientific Advisory Committee on Genetic Mechanisms in Cancer
1999 - 1999	Ad Hoc Reviewer, National Institutes of Health CBY-2 Study Section
2000 - 2001	Vice-Chair, then Chair, American Cancer Society Scientific Advisory Committee on Genetic Mechanisms in Cancer
2001 - 2001	Proposal reviewer, Ohio Board of Regents
2002 - 2002	Reviewer, Intramural site visit team, Laboratory of Metabolism, National Cancer Institute, NIH
2002 - 2004	Member, National Institutes of Health CDF3 Study Section
2005 - 2005	Reviewer, Senior Research Fellowships, The Wellcome Trust, London, UK
2006 - 2011	Reviewer, The Medical Foundation: The Charles A. King Trust Postdoctoral Research Fellowship Program, Boston, MA
2011 -	Review Editor, Frontiers in Molecular and Structural Endocrinology
2011 - 2016	Reviewer, Alzheimer's Association International Grant Program

Honors

1973	Phi Beta Kappa, Oberlin College
1974	Harry Nichols Holmes Award for excellence in chemistry, Oberlin College Chemistry Department
1975	Predoctoral Fellowship, Camille and Henry Dreyfus Foundation, Inc.

1978	NIH Predoctoral Trainee, Harvard University
1980	Postdoctoral Fellowship, Jane Coffin Childs Memorial Fund for Medical Research
1984	Basil O'Connor Starter Scholar, March of Dimes Birth Defects Foundation
1986	Junior Faculty Research Award, American Cancer Society, Inc.
1992	Faculty Research Award, American Cancer Society, Inc.
2004	Ruth L. Kirschstein Senior Fellowship Award, National Institutes of Health

C. Contribution to Science

1. **Demonstration of LSF-mediated mitotic regulation by a nontranscriptional mechanism.** Inhibition of LSF both by small molecule inhibitors (FQI1) and by siRNA causes a mitotic arrest of condensed but nonaligned chromosomes, in multiple cell types. Surprisingly, inhibition of LSF shortly prior to mitotic entry or even in mitosis also results in such an arrest, arguing against a transcriptional mechanism for this arrest. We demonstrated that the specific interaction between LSF and multiple other proteins, including α-tubulin, is disrupted by FQI1. Furthermore, FQI1 treatment of cells causes spindle defects. I was the senior investigator driving these studies.

   a. Chin HG, Ponnaluri C, Zhang G, Estève P-O, Schaus SE, Hansen U, Pradhan S. Transcription factor LSF-DNMT1 complex dissociation by FQI1 leads to aberrant DNA methylation and gene expression. Oncotarget 2016. 7:83627-83640.

   b. Chin HG, Biagi JM, Willoughby JLS, Estève P-O, Ruse C, Lee J, Schaus SE, Pradhan S, Hansen U. Lysine methylation of α-tubulin by microtubule-associated SET8 is facilitated by LSF. 2019, BioRxiv doi.org/10.1101/665984.

   c. Willoughby JLS, George K, Roberto M, Chin HG, Stoiber P, Shin H, Pedamallu CS, Schaus SE, Fitzgerald K, Shah J, Hansen U. LSF-targeted siRNAs phenocopy LSF small molecule inhibitors in causing mitotic defects, cell death and senescence in cancer cells. 2019, BioRxiv doi.org/10.1101/665570.

2. **Demonstration of cell cycle regulation at the G1/S transition by the LSF transcription factor.** Tight regulation of cell cycle progression is critical for maintenance of genomic integrity. Cell cycle-stage transcriptional control is one of the regulatory pathways that directs the ordered series of cell cycle events. In higher eukaryotes, the E2F/Rb pathway is key for regulating the G1/S transition. However, it is not the sole pathway, as we have demonstrated that LSF regulates essential G1/S genes (e.g. *Tyms*, encoding thymidylate synthase). In general, LSF is constitutively expressed at low levels, but its transcriptional and DNA-binding activities are regulated by phosphorylation downstream of multiple growth signaling pathways, including MEK/ERK and cyclin C/CDK2-3. Its activity is therefore modulated in parallel pathways to that of E2F. This similarity suggested roles for LSF dysregulation in disease, which we and others have since confirmed. I was the senior investigator driving all these studies.

   a. Volker JL, Rameh LE, Zhu Q, DeCaprio J, Hansen U. Mitogenic stimulation of resting T cells causes rapid phosphorylation of the transcription factor LSF and increased DNA-binding activity. Genes Dev. 1997 Jun 1;11(11):1435-46. PubMed PMID: 9192871.

   b. Powell CM, Rudge TL, Zhu Q, Johnson LF, Hansen U. Inhibition of the mammalian transcription factor LSF induces S-phase-dependent apoptosis by downregulating thymidylate synthase expression. EMBO J. 2000 Sep 1;19(17):4665-75. PubMed PMID: 10970859; PubMed Central PMCID: PMC302058.

   c. Saxena UH, Powell CM, Fecko JK, Cacioppo R, Chou HS, Cooper GM, Hansen U. Phosphorylation by cyclin C/cyclin-dependent kinase 2 following mitogenic stimulation of murine fibroblasts inhibits transcriptional activity of LSF during G1 progression. Mol Cell Biol. 2009 May;29(9):2335-45. PubMed PMID: 19237534; PubMed Central PMCID: PMC2668376.

   d. Hansen U, Owens L, Saxena UH. Transcription factors LSF and E2Fs: tandem cyclists driving G0 to S?. Cell Cycle. 2009 Jul 15;8(14):2146-51. PubMed PMID: 19556876; PubMed Central PMCID: PMC2796248.

3. **First definitive demonstration of repression at a distance by a eukaryotic transcription factor.**
The most transformative contribution I have made, which fundamentally altered views of transcriptional repression mechanisms, was the demonstration in 1990 that transcription factors could actively repress gene expression. Dogma at the time, based in part on models from bacterial gene regulation, was that transcriptional repression occurred by steric hindrance. That is, repressors simply precluded the binding of transcriptional activators or the RNA polymerase complex to the DNA. Indeed, in 1981 as a postdoctoral fellow, I showed for the first time transcriptional repression in a mammalian system by the SV40 T antigen binding sites near the transcriptional start site of the early SV40 promoter (coincident with the Tjian laboratory). In contrast, in the case of the *Drosophila* Kruppel protein, which genetically inhibits gene expression of other early developmental genes, my laboratory showed that transcriptional repression occurred when the repressor was bound distant from the transcriptional activators or the transcription start site. Furthermore, we demonstrated that transcriptional repression could be localized to a domain of the protein distinct from its DNA-binding domain. Our findings, subsequently shown to be a widespread property of eukaryotic transcriptional repressors, laid groundwork for understanding the role of epigenetics in gene repression with repressors recruiting corepressors that modify the histones, and generally inactivate the region of chromatin around the site. I was the major driver in all of these studies, either as the major experimentalist (postdoctoral study) or as the senior investigator in the distance-independent transcription repression studies.

   a. Hansen U, Tenen DG, Livingston DM, Sharp PA. T antigen repression of SV40 early transcription from two promoters. Cell. 1981 Dec;27(3 Pt 2):603-13. PubMed PMID: 6101224.
   b. Licht JD, Grossel MJ, Figge J, Hansen UM. Drosophila Krüppel protein is a transcriptional repressor. Nature. 1990 Jul 5;346(6279):76-9. PubMed PMID: 2114551.
   c. Licht JD, Hanna-Rose W, Reddy JC, English MA, Ro M, Grossel M, Shaknovich R, Hansen U. Mapping and mutagenesis of the amino-terminal transcriptional repression domain of the Drosophila Krüppel protein. Mol Cell Biol. 1994 Jun;14(6):4057-66. PubMed PMID: 8196644; PubMed Central PMCID: PMC358771.
   d. Hanna-Rose W, Hansen U. Active repression mechanisms of eukaryotic transcription repressors. Trends Genet. 1996 Jun;12(6):229-34. PubMed PMID: 8928228.

4. **First identification of a protein that facilitates transcriptional elongation of RNA polymerase II through chromatin in mammalian cells.**
My laboratory demonstrated in 1994 that the abundant, non-histone HMGN chromosomal proteins enhanced RNA polymerase II transcription, only on chromatin templates, by facilitating transcriptional elongation. The transcription field at that time was just beginning to appreciate that transcriptional regulation could occur not only at initiation of transcription, but also at subsequent steps, including elongation. But although it had been shown that nucleosomes dramatically inhibited elongation of RNA polymerase II, factors that overcame this blockage had not yet been identified. We demonstrated that HMGN proteins, which were associated largely with active chromatin, enhanced transcriptional elongation. In succeeding studies we extended these findings by demonstrating that HMGN proteins counteracted transcriptional repression by histone H1, which compacts chromatin. Subsequently, a number of other proteins have been demonstrated to facilitate transcriptional elongation through chromatin. I was the senior investigator leading these studies.

   a. Ding HF, Rimsky S, Batson SC, Bustin M, Hansen U. Stimulation of RNA polymerase II elongation by chromosomal protein HMG-14. Science. 1994 Aug 5;265(5173):796-9. PubMed PMID: 8047885.
   b. Ding HF, Bustin M, Hansen U. Alleviation of histone H1-mediated transcriptional repression and chromatin compaction by the acidic activation region in chromosomal protein HMG-14. Mol Cell Biol. 1997 Oct;17(10):5843-55. PubMed PMID: 9315642; PubMed Central PMCID: PMC232432.

5. **First mapping of nucleosome positions at an endogenous mammalian steroid-inducible promoter, demonstrating estrogen-inducible changes in nucleosome positioning at the TFF1 promoter.**
Although it had long been appreciated that actively transcribed genes differed significantly in their chromatin state as compared to that of inactive genes, identifying inducible changes from an inactive to an active chromatin state in response to cellular signaling pathways was a key step in furthering understanding of transcriptional induction. We performed the first in vivo detailed characterization of

chromatin structure at a natural, estrogen-responsive promoter. Key results included the demonstration of two tightly positioned nucleosomes, with a long linker region in between, and alterations in the nucleosome at the TATA box upon estrogen stimulation. We then extended our findings to demonstrate that inducible histone acetylation of the nucleosomes at the promoter enhanced binding of TBP at the TATA box. Based on our mapping data, others analyzed the interplay of transcription factor and coactivator binding, nucleosome positioning, and chromatin modifications at this promoter, demonstrating amazing complexity underlying its rapid responses to hormone. I was the senior investigator leading these studies.

a. Sewack GF, Hansen U. Nucleosome positioning and transcription-associated chromatin alterations on the human estrogen-responsive pS2 promoter. J Biol Chem. 1997 Dec 5;272(49):31118-29. PubMed PMID: 9388265.
b. Sewack GF, Ellis TW, Hansen U. Binding of TATA binding protein to a naturally positioned nucleosome is facilitated by histone acetylation. Mol Cell Biol. 2001 Feb;21(4):1404-15. PubMed PMID: 11158325; PubMed Central PMCID: PMC99592.

Complete List of Published Work in MyBibliography:

https://www.ncbi.nlm.nih.gov/sites/myncbi/ulla.hansen.1/bibliography/40096814/public/?sort=date&direction= descending