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BIOGRAPHICAL SKETCH

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NAME: Larry D. Mesner

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

POSITION TITLE: Assistant Professor, Dept. of Public Health and the Center for Public Health Genomics, University of Virginia

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 Iowa, Iowa City, IA	B.S.	1982	Botany
University of Virginia, Charlottesville, VA	Ph.D.	1992	Biochemistry

A. Personal Statement

I have spent over 25 years studying varying aspects of DNA replication and genome instability, from *in vitro* studies of polymerase elongation complexes to the development of methods for whole-genome studies in mammalian systems. I conceived of and developed an *in loco* mutagenesis method that enabled us to identify genetic elements required to initiate DNA replication in the Chinese hamster ovary DHFR locus within its native chromosomal context. These studies led us to conclude that genetic replicators, which characterize replication origins in bacteria and lower eukaryotes, either do not exist or are highly redundant in mammalian cells. These findings contributed substantially to the present consensus opinion in the field that regulation of origin activity in higher eukaryotic cells is predominantly epigenetic. On the other hand, studies of a similar nature did identified three distinct genetic elements in this locus that influence replication. Two of these affect where and how often initiation occurs by their direct effect on the promoter and, thus, transcription of the DHFR gene. These studies provided well-controlled experimental evidence that transcription precludes replication initiation on the same template, but enhances it in adjacent non-transcribed regions. A third relevant genetic element lies approximately in the center of the DHFR initiation zone and was previously identified as a matrix attachment region (MAR). Interestingly, when it was deleted, it did not affect initiation but, rather, prevented the local separation of daughter chromatids after passage of the replication fork. These studies provided important insight into a long-hypothesized aspect of nuclear organization of chromatin during DNA replication. Finally, I developed a method for isolating DNA fragments that contain the replication bubbles that are centered over initiation sites. This has allowed us to isolate most if not all of the active origins of replication in any complex genome.

In the last 7 years I have been working on developing a pipeline for verifying candidate genes from GWAS studies using mouse models coupled with human and mouse cell model systems. This involves chromatin structure and transcriptional activity evaluation followed by genome editing as the means of testing the proposed hypotheses. To this end, we have finishing up studies on the Bicc1, MARK3 and LHFP genes and are writing up a study on the Qsox1 gene and are in beginning a study of the DOCK9 gene; all where/are hypothesized to be causal in various aspects of bone physiology.

B. Positions and Honors

Assistant Professor of Research ,Dept. of Public Health and the Center for Public Health Genomics, University of Virginia, July 2013-present

Assistant Professor of Research , Dept. of Biochemistry & Molecular Genetics and The Center for Public Health Genomics, University of Virginia, Jan 2012-June 2013

Assistant Professor of Research , Dept. of Biochemistry & Molecular Genetics, University of Virginia, October 1999-Dec 2011

Research Associate with Joyce L. Hamlin, Ph.D., University of Virginia, April 1994 – October 1999

Postdoctoral Associate with Joel W. Hockensmith, Ph.D., University of Virginia, July 1992 - March 1994

Graduate Research Assistant with Joel W. Hockensmith, Ph.D., University of Virginia, July 1987 - June 1992

Research Specialist with James W. Ogilvie, Ph.D., University of Virginia, August 1983 - August 1986

Research Specialist with Jiwan P. Palta, Ph.D., University of Wisconsin-Madison, July 1982 - July 1983

Scholarships and Fellowships:

Iowa Scholastic Achievement Scholarship, September 1979 - May 1982

Predoctoral Trainee, Dept. of Health and Human Services Public Health Service Grant # 5-T32-GM08136, July 1986 - June 1989

Postdoctoral Trainee, Dept. of Health and Human Services Public Health Service Grant # 5-T32-CA09109-21, July 1995 - June 1997

C. Contributions to Science

Publications:

Mesner, L. D., Sutherland, W. M. and Hockensmith, J. W. (1991). DNA-dependent adenosinetriphosphatase A is the eukaryotic analog of the bacteriophage T4 Gene 44 Protein: immunological identity of DNA replication-associated ATPases. *Biochemistry* **30**, 11490-11494.

Mesner, L. D. and Hockensmith, J. W. (1992). Probing the energetics of Oligo(dT)·Poly(dA) by laser cross-linking. *Proc. Natl. Acad. Sci. USA* **89**, 2521-2525.

Mesner, L. D., Truman, P. A. and Hockensmith, J. W. (1993). DNA-dependent adenosinetriphosphatase A: immunoaffinity purification and characterization of immunological reagents. *Biochemistry* **32**, 7772-7778.

Hockensmith, J. W., Kubasek, W. L., Evertsz, E. M., Mesner, L. D., and von Hippel, P. H. (1993). Laser crosslinking of proteins to nucleic acids: II. interactions of the bacteriophage T4 DNA replication polymerase accessory proteins complex with DNA. *J. Biol. Chem.* **268**, 15721-15730.

Kalejta, R. F., Li, X., Mesner, L. D., Dijkwel, P. A., Lin, H. –B., and Hamlin, J. L.(1998). Distal sequences, but not *ori-∃*/ OBR-1, are essential for initiation of DNA replication in the Chinese hamster DHFR origin. *Mol. Cell* **2**, 797-806.

Muthuswami, R., Truman, P.A., Mesner, L.D., and Hockensmith, J.W.(2000). An eukaryotic SWI2/SNF2 domain, an exquisite detector of double-stranded to single-stranded DNA transition elements. *J Biol Chem **275**, 7648-7655*.

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Muthuswami, R., Mesner, L.D., Wang, D., Hill, D.A., Imbalzano, A.N., and Hockensmith, J.W.(2000). Phosphoaminoglycosides inhibit SWI2/SNF2 family DNA-dependent molecular motor domains. *Biochemistry **39**, 4358-4365.*

Singer*, M. J., Mesner*, L. D., Freidman, C. J., Trask, B. J. and Hamlin, J. L.(2000). Amplification of the human dihydrofolate reductase gene via double minutes is initiated by chromosomal breaks. *Proc. Natl. Acad Sci.USA **97**, 7921-7926.*

Mesner, L.D., Li, X., Dijkwel, P.A., and Hamlin, J.L.(2003). The dihydrofolate reductase origin of replication does not contain any nonredundant genetic elements required for origin activity. *Mol. Cel. Biol.* **23**, 804-814.

Mesner, L.D., Hamlin, J.L., and Dijkwel, P.A. (2003). The matrix attachment region in the Chinese hamster dihydrofolate reductase origin of replication may be required for local chromatid seperation. *Proc. Natl. Acad Sci.USA* **100**, 3281-3286.

Saha, S., Shan Y., Mesner, L.D., and Hamlin, J.L. (2004). The promoter of the Chinese hamster ovary dihydrofolate reductase gene regulates the activity of the local origin and helps define its Boundaries. *Genes Dev.* **18**, 397-410.

Mesner, L.D., and Hamlin, J.L. (2005). Specific signals at the 3' end of the DHFR gene define one boundary of the downstream origin of replication. *Genes Dev.* **19**, 1053-1066.

Wong, T. E., Kolman, J.L., Li, Y-C., Mesner, L.D., Hillen, W., Berens, C., and Wahl, G.M. (2005). Reproducible doxycycline-inducible transgene expression at specific loci generated by Cre-recombinase mediated cassette exchange. *Nuc. Acids Res.***33**, e147.

Mesner, L.D., Crawford, E.L., and Hamlin, J.L. (2006). Isolating apparently pure libraries of replication origins from complex genomes. *Mol. Cell* **21**, 719-726.

Hamlin, J.L., Mesner, L.D., Lar, O., Torres, R., Chodaparambil, S.V., and Wang, L. (2008). A revisionist replicon model for higher eukaryotic genomes. *J. Cell. Bioc.* **105**, 321-329.

Mesner, L.D., Dijkwel, P.A. and Hamlin, J.L. (2009). Purification of restriction fragments containing replication intermediates from complex genomes for 2-D gel analysis. *Methods Mol. Biol.* **521**, 121-137.

Mesner, L.D., and Hamlin, J.L. (2009). Isolation of restriction fragments containing origins of replication from complex genomes. . *Methods Mol. Biol.* **521**, 315-328.

Guasconi, V., Pritchard, L-L., Fritsch, L., Mesner, L.D., Francastel, C., Harel-Bellan, A., and Ait-Si-Ali, S. (2010). Preferential association of irreversibly silenced E2F-targeted genes with pericentric heterochromatin in differentiated muscle cells. *Epigenetics* **5**, 704-709.

Hamlin, J.L., Mesner, L.D. and Dijkwel, P.A. (2010). A winding road to origin discovery. *Chromosome Res.* **18**, 45-61.

Mesner, L.D., Valsakumar, V., Karnani, N., Dutta, A., Hamlin, J.L., Bekiranov, S. (2011). Bubble-chip analysis of human origin distributions demonstrates on a genomic scale significant clustering into zones and significant association with transcription. *Genome Res.* **21**:377-389 (PubMed Central PMCID: PMC3044852)..

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Farber, C.R., Mesner, L.D. (2016). A Systems-level Understanding of Cardiovascular Disease through Networks. Annabelle Rodriguez-Oquendo (ed), Translational Cardiometabolic Genomic Medicine, 59-81.

Calabrese, G., Mesner, L. D., Foley, P. L., Rosen, C. J., & Farber, C. R. (2016). Network Analysis Implicates Alpha-Synuclein (Snca) in the Regulation of Ovariectomy-Induced Bone Loss. *Scientific Reports*, *6* (PMCID: PMC4932518)

Calabrese, G. M., Mesner, L. D., Stains, J. P., Tommasini, S. M., Horowitz, M. C., Rosen, C. J., & Farber, C. R. (2017). Integrating GWAS and Co-expression Network Data Identifies Bone Mineral Density Genes SPTBN1 and MARK3 and an Osteoblast Functional Module. *Cell systems*, *4*(1), 46-59 (PMCID:PMC5269473)

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