BIOGRAPHICAL SKETCH

Senior Trainer.

NAME: Joan S. Jorgensen

eRA COMMONS USER NAME: JORGENSEN_JOAN

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 Wisconsin, Madison, WI	B.S.	1988	Biochemistry
University of Wisconsin, Madison, WI	D.V.M	1993	Veterinary Medicine
North Carolina State University, Raleigh, NC - Internship & Residency, Board Certification	A.C.V.I.M	1997	Veterinary Internal Medicine
Case Western Reserve University	Ph.D.	2001	Pharm/Endocrinology

A. Personal Statement

After obtaining my baccalaureate degree, I pursued professional and clinically oriented educations. After obtaining my DVM and completing a residency in Equine Internal Medicine, I focused on basic science research, receiving my doctoral degree in molecular endocrinology. From these experiences I have become a clinician scientist with great appreciation for both basic science and clinical medicine.

My laboratory's investigations into female and male gonad development are inspired by the quest to understand the fetal basis of sex-specific adult diseases in reproductive endocrinology. Our interest in female gonad development is focused on formation of the unique cellular niche, the follicle, which ensures survival and maturation of the female gamete. We discovered a cluster of homeobox transcription factors that are expressed during ovary development whose disruption results in follicle failure and oocyte death, classic components of premature ovarian failure, a devastating disease in adult females. Our interest in *male gonad development* is centered on *local* regulation of androgen synthesis. Defective androgen synthesis or activity during fetal development is emerging as a component of adult male infertility and decreased virility. Historically, local control of androgenesis was thought to be unique to the developing testis; however, aggressive forms of prostate cancer are now also known to acquire this capacity. Since this discovery, we have parlayed our tools and knowledge of fetal testis androgen synthesis to prostate cancer and demonstrated that prostate cancer cells use similar mechanisms to stimulate androgen production that fuels deadly castration resistant prostate cancer. The major goals of my research have been to discover local cell-cell interactions and molecular mechanisms that are used to establish the nascent ovarian follicle niche, control the onset and maintenance of fetal testosterone synthesis, and stimulate the acquisition of steroidogenic activity within rogue cancer cells.

B. Positions and Honors

Positions and Employment

1989-1993 Veterinary Student, School of Veterinary Medicine, University of Wisconsin, Madison, WI
1993-1994 Intern, Equine Ambulatory Medicine, College of Veterinary Medicine, North Carolina State University, Raleigh, NC
1994-1996 Resident, Equine Internal Medicine, College of Veterinary Medicine, North Carolina State University, Raleigh, NC
1996-2001 Predoctoral Research, Professor John H. Nilson, Department of Pharmacology, Case Western

Reserve University, Cleveland, OH
2001-2002 Postdoctoral Research, Professor John H. Nilson, Department of Pharmacology, Case Western Reserve University, Cleveland, OH
2002-2008 Assistant Professor**,** Department of Veterinary Bioscience, University of Illinois, Urbana, IL
2008-2014 Assistant Professor, Department of Comparative Biosciences, University of Wisconsin, Madison, WI
2014- Associate Professor, Department of Comparative Biosciences, University of Wisconsin, Madison, WI

Professional Memberships and Other Experiences

1997- Member, American College of Veterinary Internal Medicine
2000- Member, Society for the Study of Reproduction (SSR)
2000- Member, The Endocrine Society
2000- Member, Women in Endocrinology
2008- Advisor, Trainee Affairs Committee, SSR
2010- Member, Public Affairs Committee, SSR
2013- Editorial board, Biology of Reproduction
2013- Faculty Member, Frontiers in Reproduction
2014 Early Stage Reviewer for National Institutes of Health, Cellular, Molecular and Integrative Reproduction Study Section (NIH-CMIR)
2015-2021 Standing Study Section Member, NIH-CMIR

Honors

2004 Arnold O. Beckman Research Award, University of Illinois
2007 Carl J. Norden/Pfizer Distinguished Teaching Award, University of Illinois
2007 Dr. Gordon & Mrs. Helen Kruger Distinguished Teacher Award, University of Illinois
2015 Nominated Zoetis Teaching Award, University of Wisconsin-Madison

C. Contribution to Science

1. My dissertation studied the mechanisms that sex steroids use to provide negative feedback on the two subunit genes (αGSU and LHβ) that combine to form luteinizing hormone (LH). My studies showed that the androgen receptor (AR) suppressed both promoters by interacting with specific transcription factors that are required for individual gene expression. To suppress activity of the αGSU promoter, AR interacted with two bZIP proteins that bind cyclic AMP responsive elements (CREs), namely, cJUN and ATF2. Furthermore, overexpression of cJUN and ATF2 expression vectors attenuated the suppressive effect of AR on the αGSU promoter. Alternatively, AR suppressed the LHβ promoter by interacting with the orphan nuclear receptor, SF1 (NR5A1). However, the addition of EGR1 and PITX1, proteins critical for LHβ gene expression, disrupted the binary complex that contains AR and SF1. These studies not only identified distinct mechanisms of AR mediated repression for the αGSU and LHβ genes, but they also uncovered two novel AR interacting proteins, ATF2 and SF1.
   a. **Jorgensen JS**, Nilson JH 2001 Androgen receptor suppresses transcription of the α glycoprotein subunit gene through protein-protein interactions with cJun and ATF2. Mol Endocrinol 15(9):1496-1504.
   b. **Jorgensen JS**, Nilson JH 2001 Androgen receptor suppresses the luteinizing hormone β subunit by interacting with SF1. Mol Endocrinol 15(9):1505-1516,
   c. Chipuk JE, Cornelius SS, Pultz NJ, **Jorgensen JS**, Bonham MJ, Kim SJ, Danielpour D 2002 The androgen receptor represses TGF-beta signaling through interaction with Smad3. J Biol Chem 277(2):1240-8.
   d. **Jorgensen JS**, Quirk CC, Nilson JH 2004 Multiple and overlapping combinatorial codes orchestrate hormonal responsiveness and dictate cell-specific expression of the genes encoding LH. Endocr Rev 25:521-542.

2. After germ cells colonize the developing ovary, cord-like structures emerge while somatic cells surround clusters of rapidly dividing germ cells to form germline cysts. This cord-like structure provides the basic and critical infrastructure to support homo- and heterotypic communication networks between

germ and somatic cells. We evaluated ovaries from two mouse models, the *Fused Toes* (6 deleted genes: *Irx3,-5,-6, Fts, Fto, Ftm*) and *Irx3*$^{-/-}$;*Irx5*$^{GFP/GFP}$ double knockout mouse models (*Irx3*$^{-/-}$ and *Irx5*$^{-/-}$ single knockouts were fertile), and learned that *Irx3/5* are dispensable for ovary and follicle formation; however, nascent primordial follicles failed to thrive and oocytes died within days of follicle formation. Closer examination pointed to disruption of communication networks that facilitated germ-somatic cell communication within germline cysts and new follicles. New preliminary data suggest that IRX3/5 regulate gap junction genes, *Gja1* and *-5* (connexins 43, 40), among other cell-cell interactors. Our studies highlight IRX3/5 as new factors that mediate critical somatic-germ cell communication and suggest that the very first interactions between these cells within germline cysts and primordial follicles establish granulosa cell and oocyte identities that are required to preserve follicle and oocyte health.

a. **Jorgensen JS**, Gao L 2005 *Irx3* Is Differentially Up-regulated in Female Gonads During Sex Determination Gene Expr Patterns 5/6:756-762.
b. Kim B, Kim Y, Sakuma R, Hui CC, Rüther U, **Jorgensen JS** 2011 Primordial germ cell proliferation is impaired in Fused Toes mutant embryos. Dev Biol 349:417-426. PMCID: In progress.
c. Kim B, Kim Y, Cooke PS, Rüther U, **Jorgensen JS** 2011 The Fused Toes locus is essential for somatic-germ cell interactions that foster germ cell maturation in developing gonads. Biol Reprod 84:1024-32. PMCID: In progress.
d. **Jorgensen JS**. 2013 Defining the neighborhoods that escort the oocyte through its early life events and into a functional follicle. *Mol. Reprod. Dev.,* 80:960-976. PMID: 24105719. PMC3980676.

3. We approach local androgen synthesis in the developing testis and aggressive prostate cancer cells as two examples of gonadotropin-independent steroidogenesis and have focused on investigating SF1 regulation and activity as a common mediator in both situations. In the fetal testis, we combined bioengineering platforms and genetic mouse models and can now successfully culture fetal Leydig cells within microfluidic chambers in both mixed and pure populations that mimic physiologically relevant cell-cell interactions on a microscale. In addition, we established a technique using microinjection and electroporation to investigate regulation of genes within the developing gonad, specifically for factors including *Sf1* and hedgehog signaling pathways. Together, our studies have provided significant tools to advance the study of fetal Leydig cells and have identified specific factors that regulate SF1 and affect testosterone production in the fetal testis. Concurrent with our fetal testis work, we discovered that SF1, which is not normally found in the prostate, is expressed in late stage, aggressive prostate cancers. Using *in vitro* culture and *in vivo* xenograft systems, we found that SF1 stimulates new steroid synthesis and increases proliferation to fuel deadly tumor growth. Our studies implicate normal developmental and endocrinological roles of SF1 in aberrant steroid production within rogue prostate cancer cells, thereby illuminating a potential new drug target.
   a. Barsoum IB, Bingham NC, Parker KL, **Jorgensen JS**, Yao HHC 2009 Activation of the Hedgehog pathway in the mouse fetal ovary leads to ectopic appearance of fetal Leydig cells and female pseudohermaphroditism. Dev Biol 329(1):96-103. PMCID: PMC2673990
   b. Gao L, Kim B, Kim Y, Lofgren SM, Schultz-Norton JR, Nardulli AM, Heckert LL, **Jorgensen JS** 2011 Two regions within the proximal Sf1 promoter drive somatic cell-specific activity in developing gonads of the female mouse. Biol Reprod 84:422-434. PMCID: PCM3043126.
   c. Lewis SR, Hedman CJ, Ziegler T, Ricke WA, **Jorgensen JS**. 2014 Steroidogenic Factor 1 promotes aggressive growth of castration resistant prostate cancer cells by stimulating steroid synthesis and cell proliferation. *Endocrinology.* 155(2):358-69. doi:10.1210/en.2013-1583**.** PMID: 24265454
   d. Carney CM, Muszynski JL, Strotman LN, Lewis SR, O'Connell RL, Beebe DJ, Theberge AB, **Jorgensen JS**. 2014 Cellular microenvironment dictates androgen production by murine fetal Leydig cells in primary culture. *Biol. Reprod.* 91(4):85. doi.114.118570. PMID: 25143354

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/joan.jorgensen.1/bibliography/40694429/public/?sort=date&direction=ascending

D. Research Support

Grant Support-Current

NIH R01HD075079 Jorgensen (PI) 04/01/13 – 03/31/18
IRXB Factors Direct Follicle Formation
The fundamental hypothesis guiding this proposal is that Iroquois homeobox transcription factors, *Irx3/5*, which are tightly regulated by βcatenin, coordinate somatic cell-oocyte communication to promote oocyte survival and early stages of follicle maturation. Inducible mouse models will be used to knockout and knock-in gonad *Irx3/5* activity to identify their critical juncture of temporal and spatial expression that promotes oocyte health and survival. Then, *Irx3/5* regulation by βcatenin will be evaluated to uncover a novel pathway, βcatenin-*Irx3/5*, in the control of oocyte-granulosa cell communication whose disruption may contribute to causes of infertility and premature ovarian failure.
Role: PI

NIH NCI P30 CA014520 Jorgensen Pilot Project PI 04/01/16 - 03/31/17
University of Wisconsin Carbone Cancer Center (UWCCC) Pilot Projects
SF1 expression predicts synthesis and response to abiraterone therapy in CRPC
Aggressive castration resistant prostate cancer (CRPC) is notoriously difficult to treat. Recent efforts have centered on anti-androgen receptor (AR) therapy in combination or sequential to steroid synthesis inhibition along with other forms of chemotherapy. Despite the recent breakthroughs in clinical therapy options for aggressive prostate cancer, however, outcomes are highly variable and resistance develops rapidly. Steroidogenic Factor 1 (SF1, NR5A1) is an established regulator of steroidogenesis, including *Cyp17a1* and *3βHSD*, in normal endocrine organs; we recently discovered that it also stimulates steroid synthesis in CRPC xenografts[7]. Therefore, this proposal is designed to test they hypothesis that the presence of SF1 identifies aggressive prostate cancers and predicts their response to abiraterone therapy.
Role: PI for Pilot Project