OMB No. 0925-0001/0002 (Rev. 08/12 Approved Through 8/31/2015)

BIOGRAPHICAL SKETCH

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NAME: Jon Oatley

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

JONOATLEY POSITION TITLE: Associate Professor & Director

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 Nevada, - Reno, NV	B.S.	05/99	Animal Sciences
Washington State University, Pullman, WA	M.S.	06/01	Reproductive Biology
Washington State University, Pullman, WA	Ph.D.	05/04	Reproductive Biology
University of Pennsylvania, Philadelphia, PA	Postdoc	06/07	Reproductive/Stem Cell Biology

A. PERSONAL STATEMENT

The majority of my research career has focused on the regulation of undifferentiated spermatogonial maintenance and differentiation in mammals primarily using mice as a model for human biology. During postdoctoral studies with Dr. Ralph Brinster, I gained skills for isolating spermatogonial stem cells and examining their fate regulation using molecular biology, transgenic biology, and transplantation methodologies. My postdoctoral studies were among the first to identify critical genes regulating the maintenance of spermatogonial stem cells and revealed key cytokines that specifically influence the self-renewal fate decision. As an independent investigator, my lab has continued to functionally decipher the molecular pathways that regulate the stem cell and progenitor states in mammalian spermatogonia. We are also keenly interested in defining molecular and phenotypical features that distinguish the spermatogonial subtypes. Recently, we have begun exploring the pathways guising establishment of the foundations stem cell pool in the male germline during late fetal and early neonatal development. To address research questions of the central concepts, we have honed the skills for isolating spermatogonial stem cells, maintaining the cells in vitro for extended periods of time, manipulating molecular pathways in the cells, and transplanting the cells to determine effects on biological function. We have made the seminal discovery that stem cells express the transcriptional repressor ID4 and generated a unique mouse model in which the cells are marked by expression of EGFP. The *Id4- eGfp* transgenic mouse model is a critical tool in the field that allows for studying stem cells and progenitors separately which has never before been achievable.

B. POSITIONS AND

HONORS <u>Positions and</u>

<u>Employment</u>

2014- Associate Professor, School of Molecular Biosciences, College of Veterinary Medicine, Washington State University
2013- Director, Center for Reproductive Biology, Washington State University
2011-2014 Assistant Professor, School of Molecular Biosciences, College of Veterinary Medicine, Washington State University

2010-2011 Adjunct Assistant Professor, Department of Cellular and Molecular Physiology, College of Medicine, Pennsylvania State University

2007-2011 Assistant Professor of Reproductive Biology, Department of Dairy and Animal Sciences, Pennsylvania State University

2004-2007 Postdoctoral Fellow/Research Associate, University of Pennsylvania, Department of Animal Biology, School of Veterinary Medicine, Laboratory of Reproductive Physiology. Advisor: Dr. R.L. Brinster

1999-2004 Ph.D. in Animal Sciences, Washington State University, Department of Animal Sciences. Advisors: Dr. J.J. Reeves and Dr. D.J. McLean

Other Experience and Professional Memberships

2013-Present American Society of Andrology
2004-Present Society for the Study Reproduction
1998-2007 American Society of Animal Sciences

Honors and Awards

2015 Young Andrologist Award – American Society of Andrology
2014 Dean's Award for Outstanding Research – Washington State University
2012 New Investigator Award – Society for the Study of Reproduction (SSR)
2012 Ralph Yount Excellence in Research Award – Washington State University
2011 Frontiers in Reproduction Lecturer
2010 Barron Lectureship in Reproductive Physiology – University of Florida
2004 USDA NRI Merit Award
2001-2002 Blosser Graduate Fellowship – Washington State University
2002, 2004 PhD Graduate Student of the Year – Washington State University
2002-2004 Achievement Reward for Collegiate Scientists Fellowship – Washington State University

Professional Service

2015-Present Standing Member, NIH Cell and Molecular Integrated Reproduction (CMIR) Study Section
2011-Present Board of Reviewing Editors, Biology of Reproduction
2011-Present Board of Reviewing Editors, Spermatogenesis Journal
2011-Present Chair of SSR Membership Committee

C. CONTRIBUTION TO SCIENCE

1. Molecular Mechanisms that Influence Maintenance of the Stem Cell State in Mammalian Spermatogonia

The activities of the spermatogonial population provides a foundation for continuity of the spermatogenic lineage and is a heterogeneous mix of subtypes including rare stem cells with regenerative capacity, transit amplifying progenitors, and differentiating subtypes. A major portion of my studies has addressed the gap in knowledge of key molecular mechanisms that influence the fate decisions of these subtypes. My postdoctoral studies were among the first to use transcriptome profiling for identifying genes that potentially regulate spermatogonial stem cell (SSC) fates and I began assigning biological relevance to many of these. To carry out functional analyses, I established methodology for utilizing RNA interference to knockdown expression of specific genes and combine with transplantation analyses to assay for impaired SSC maintenance. This experimental approach is now used by several labs worldwide to assess the role of specific genes in regulating SSC functions. My initial postdoctoral studies identified the transcription factors BCL6B, ETV5, and LHX1 as key regulators of SSC self-renewal and to this day they are widely used by other investigators as biomarkers for impaired SSC maintenance. Early in my independent career, I began mining the transcriptome datasets produced during postdoctoral studies and identified the helix-loop-helix family transcription factors NEUROG3, SOHLH1, and ID4 as potential regulators of spermatogonial fates. Through a series of functional analyses we discovered that NEUROG3 influences development of the progenitor population that arises from the SSC pool and that ID4 influences the self-renewal of SSCs. At the same

time, another group defined a role for SOHLH1 as a regulator of progenitor function similar to NEUROG3. To date, ID4 is widely regarded by the field as a key regulator of SSC self-renewal while NEUROG3 and SOHLH1 are considered regulators of the progenitor pool. In recent years, we have begun to explore the mechanisms of SOHLH1, NEUORG3, and ID4 influence on SSC and progenitor spermatogonial fates in more depth including testing of the model that the ID4 represses NEUORG3 and SOHLH1 activities to sustain the stem cell state. In addition to these transcription factors, we have discovered that the micro RNA cluster miR221/222 is involved in regulating the transition from an undifferentiated to differentiating state in spermatogonia. This finding has been widely regarded as the first definitive evidence of a role of micro RNAs in spermatogonial fates. The following major peer reviewed publications have been produced from my studies on molecular mechanisms regulating fate decisions of spermatogonia as a postdoctoral scholar and then an independent investigator:

a. **Oatley JM**, Avarbock MR, Telaranta AI, Fearon DT, Brinster RL. 2006. Identifying genes important for spermatogonial stem cell self-renewal and survival. Proc. Natl. Acad. Sci. USA 103: 9524-9529. PMID: 16740658.
b. **Oatley JM**, Avarbock MR, Brinster RL. 2007. Glial cell line-derived neurotrophic factor regulation of genes essential for mouse spermatogonial stem cell self-renewal is dependent on Src family kinase signaling. J. Biol. Chem.; 282: 25842-25851. PMID: 17597063.
c. Oatley MJ, Kaucher AV, Racicot KE, **Oatley JM.** 2011. Inhibitor of DNA binding 4 is expressed selectively by single spermatogonia in the male germline and regulates the self-renewal of spermatogonial stem cells in mice. Biol. Reprod. 85: 347-356. PMID: 21543770.
d. Kaucher AV, Oatley MJ, **Oatley JM.** 2012. Neuorg3 is a critical downstream effector of Stat3-regulated differentiation mammalian stem and progenitor spermatogonia. Biol Reprod. 86: 1-11. PMID: 22378757.
e. Yang QE, Racicot KE, Kaucher AV, Oatley MJ, **Oatley JM.** 2013. MicroRNAs 221 and 222 regulate the undifferentiated state in mammalian male germ cells. Development 140: 280-90. PMID: 23221369.

2. Molecular and Functional Dissection of Stem Cell and Progenitor Spermatogonia

Major bottlenecks in the field of spermatogenesis has been lack of molecular markers that distinguish the different spermatogonial subtypes as well as a lack in understanding of defining functional differences. During the early years as an independent investigator while studying the role of ID4 in spermatogonial stem cell (SSC) fate decisions, we made a defining observation that expression appeared to be restricted to a rare subset of the type A single spermatogonia. This Asingle population has been consider to represent the SSC pool in mammalian testes for several decades, yet markers that distinguish the cells from the more abundant transit amplifying progenitors and differentiating spermatogonia had not been reported. To study the ID4+ population in more detail, we generated a novel transgenic mouse line that possess an *Id4-eGfp* reporter transgene. We discovered that ID4-EGFP expression is restricted to a subset of the Asingle population that has high regenerative capacity thereby fitting the bill of being a marker of the SSC pool; whereas, the ID4-GFP- spermatogonial populations have limited regenerative capacity. At present, ID4 is consider the most exclusive marker of SSCs in mouse testes and the ID4-GFP line is being used by a multitude of labs in both US and international institutions to study spermatogonial population in greater depth. The following major peer reviewed publications have been produced from studies of the *Id4-eGfp* mouse line:

a. Hammoud SS, Low DHP, Yi C, Lee CL, **Oatley JM**, Payne CJ, Carrell DT, Guccione E, Cairns BR. 2015. Transcription and Imprinting Dynamics in Developing Postnatal Male Germline Stem Cells. Genes Dev. 29: 2312-24.
b. Hermann BP, Mutoji K, Velte EK, Ko D, **Oatley JM**, Geyer CB, McCarrey JR. 2015. Transcriptional and translational heterogeneity among neonatal mouse spermatogonia. Biol. Reprod. 92: 54. PMID: 25568304.
c. Chan F, Oatley MJ, Kaucher AV, Yang QE, Bieberich CJ, Shashikant CS, **Oatley JM.** 2014. Functional and molecular features of the Id4+ germline stem cell population in mouse testes. Genes Dev. 28: 1351-1362. PMID: 24939937.

3. Identification of Critical Components of the Germline Stem Cell Niche in Mammalian Testes

Stem cells in most, if not all, tissue are influenced by a cognate niche microenvironment that consists of a milieu of extrinsic factors secreted by support cell populations. A major gap in knowledge for the

field of testis biology has been the key components that constitute the spermatogonial stem cell (SSC) niche including extrinsic factors and somatic support cells. As a postdoctoral scholar, my studies identified the cytokine colony stimulating factor 1 (CSF) as an extrinsic signal that influences the self- renewal of SSCs and we localized expression to the Leydig and myoid cell populations. This finding was the first to implicate the Leydig and myoid cells as contributors to the SSC niche. For many somatic stem cell systems, there is a single support cell population that orchestrate the niche. As an independent investigator, my lab has aimed to identify the orchestrator of SSC niches in mammalian testes. Combining experimental approaches for altering the number Sertoli cells in mouse tests and transplantation of SSCs, we discovered that Sertoli cells are the orchestrator of SSC niches. The following major peer-reviewed publications have been produced from my studies on defining the key determinants of the stem cell niche in mammalian testes as a postdoctoral scholar and independent investigator:

a. **Oatley JM,** Oatley MJ, Avarbock MR, Tobias JW, Brinster RL. 2009. Colony stimulating factor 1 is an extrinsic regulator of mouse spermatogonial stem cell self-renewal. Development 136: 1191-1199.
b. Oatley MJ, Racicot KE, **Oatley JM.** 2011. Sertoli cells dictate spermatogonial stem cell niches in the mouse testis. Biol. Reprod. 84: 639-645. PMID: 21084712.

4. Mechanisms Controlling Formation of the Stem Cell Pool in Mammalian Testes

Although a stem cell pool is known to exist for the mammalian male germline, the molecular mechanisms and kinetics controlling its formation are largely undefined. The spermatogonial stem cell (SSC) population arises during a defined period of postnatal development from quiescent precursors termed prospermatogonia. As an independent investigator, my lab has aimed to identify key molecular mechanisms regulating this process. Our studies have focused on the role of Retinoblastoma protein (RB) and the instigator of this interest was the early observation that ID4 physically interacts with RB in a subset of spermatogonia in late fetal and early neonatal life. To explore a functional role, we generated mice with conditional inactivation of the Rb gene beginning at the prospermatogonial state. A single round of spermatogenesis was found to occur in these mice followed by complete loss of the germline. In addition, we discovered that renewal of the spermatogonial population following the first round of differentiation during postnatal development is impaired in an Rb deficient state. Based on these findings, we have concluded that RB is required for the formation of a self-renewing spermatogonial population during establishment of the spermatogenic lines (i.e. formation of an SSC pool). In addition to these studies, we have been using the Id4-Gfp transgenic mice to explore the kinetics of SSC pool formation. We have produced preliminary evidence that a subset of the prospermatogonial precursor pool serves as a seed population for the formation of the ID4+ SSC pool. A major future direction of my lab is exploring the mechanism of RB influence in greater depth and defining the kinetics of SSC pool formation using the Id4-Gfp transgenic mouse model. The following major peer-reviewed publications have been produced from studies exploring formation of the SSC pool:

a. Yang QE, Gwost I, Oatley MJ, **Oatley JM.** 2013. Retinoblastoma protein (RB1) controls fate determination in stem cells and progenitors of the mouse male germline. Biol Reprod. 89: 113. PMID: 24089198.

5. Service to Advance the Broader Field of Reproductive Sciences

Beyond my impact as a basic researcher, I have made major contributions to advance the broader field of reproductive sciences. I have served as chair of the membership committee for the Society for the Study of Reproduction (SSR) since 2011 and will be the co-chair of the 2018 Gordon conference on Mammalian Reproduction. In addition, I have participated as an ad hoc reviewer on the Cell and Molecular Integrated Reproduction (CMIR) study section of NICHD and was recently nominated and approved as a standing member for 2015-2021.

Complete list of my peer-reviewed work:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1HYmc6SDXlM/bibliography/40239462/public/?sort=date&direction=ascending

D. RESEARCH SUPPORT

Ongoing

R01 061665 **Oatley (PI)** **04/01/15 – 03/31/2020**
NIH/NICHD
Control of Spermatogonial Stem Cell Fate Decisions by HLH Factors
This project is aimed at deciphering the role the specific HLH transcription regulators in the self-renewal and differentiation of spermatogonial stem cells in mouse testes. Results of these studies have advance the knowledge of adult stem cell biology and the foundational processes of spermatogenesis.

2013-00816 **Oatley (PI)** **09/01/13 – 08/31/16**
USDA/NIFA
Transplantation of spermatogonial stem cells in livestock
This project is aimed at developing methodology for transplantation of spermatogonial stem cells between male cattle.

Genus PIC **Oatley (PI)** **07/01/11 – 06/31/18**
Industry Sponsor
Culture of livestock spermatogonial stem cells
This project is aimed at refining culture conditions for the long-term expansion of spermatogonial stem cells from the testes of cattle and pigs.

R01 036745 Arnheim (PI), **Oatley (Co-PI)** **09/01/14 – 08/31/18**
NIH/NIGMS
Genetic analysis using sperm typing
The major goal of this project is to study whether spermatogonial stem cells possessing gain-of-function mutations in the Ret and Fgfr2 genes confer a selective advantage to outcompete wild-type counterparts.

R01 HD083177 Hunt (PI), **Oatley (Co-I)** **08/01/15 – 07/31/20**
NIH/NIEHS
Male Germline Development and Estrogenic Exposures
The major goal of the project is to assess the impact of estrogenic exposure during neonatal development on epigenetic modifications in spermatogonial stem cells.

Completed

R01 061665 **Oatley (PI)** **9/30/09 – 7/31/2015**
NIH/NICHD
Control of Spermatogonial Stem Cell Fate Decisions by HLH Factors

2008-00546 **Oatley (PI)** **08/01/08 – 07/31/12**
USDA NRI
Culture of Bovine Spermatogonial Stem Cells

R21 HD058137 **Oatley (PI)** **08/01/09 – 07/31/11**
NIH/NICHD