BIOGRAPHICAL SKETCH

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NAME: Karen Schindler

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

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
Loyola University Maryland	B.S.	05/99	Biology
Thomas Jefferson University	Ph.D.	07/05	Biochemistry and Molecular Biology
University of Pennsylvania	Postdoctoral	12/11	Reproductive Biology

A. Personal Statement

Since starting at Rutgers University in 2012, I have established 3 priority research focus areas in my lab that are centered around identifying and understanding the genetic causes of maternal aneuploidy. Understanding the origins of aneuploidy are important to human health because aneuploidy is the leading genetic abnormality that can lead to early miscarriage, infertility, developmental disorders, and it is a common feature in cancer. The first area involves basic science investigations into the functions of the Aurora protein kinases in mouse oocyte meiosis. Using mouse genetics and single-cell cell biology approaches we established AURKC as a major regulator of oocyte meiosis, determined meiosis-specific AURKB requirements in oocytes, and discovered an inter-Aurora kinase regulatory network required for successful female mammalian meiosis (a). The second area focuses on identifying the gene variants associated with maternal gamete aneuploidy in humans, the focus of this R01 renewal application. With access to maternal whole exome sequences and patient-specific aneuploidy data, we have identified gene variants that predispose women to high levels of gamete aneuploidy at earlier than average ages (b). And, the third area, that is under development, uses Sirtuin 7 and Aurora kinase B mouse models of premature reproductive aging to understand mechanisms that are protective of the reproductive lifespan in women (c-d).

At Rutgers, I am committed to creating and maintaining a community of Reproductive Biologists to facilitate PI and lab interactions, support trainees, and to develop collaborations. To this end, I established a Germ Cell Biology Interest Group in 2017 that currently meets monthly with 7 labs that participate. During these meetings either a trainee or outside guest speaker presents their work and the group engages in lively discussions. I established a Mammalian Reproductive Biology journal club amongst 4 labs to support our trainees in receiving up-to-date knowledge in areas of gamete, ovary and testes biology. I am also committed to improving our imaging infrastructure. I became faculty director of the HGI's imaging core in 2019 and have since added state of the art microscopes such as the Leica tauSTED nanoscopy system and recruited an imaging expert to run the daily operations and to continue building the core.

Ongoing and recently completed projects that I would like to highlight include:

1. R35-GM136340 9/2020-7/2025
   Schindler (PI)
   Signaling mechanisms that control chromosome segregation during female meiosis.

2. R35-GM136340-S1 5/2021-5/2023
   Schindler (PI)
   Diversity supplement

3. R01-HD091331 12/2017-11/2022 NCE June 2023
   Schindler (MPI)
   Association of the maternal exome with risk of an aneuploid conception

4. NIH R01 GM112801 07/2015-6/2021 (completed)
   Schindler (PI)
   Control of mammalian meiosis I through protein kinase signaling

Citations:

a. Nguyen AL, Drutovic D, Vazquez B, El Yakoubi W, Gentilello AS, Malumbres M, Solc P, **Schindler K**. (2018). Genetic interactions between the Aurora kinases reveal new requirements for AURKB and AURKC during oocyte meiosis. *Current Biology*. 28(21): 3458-68. PMCID: PMC6234855

b. Tyc KM*, El Yakoubi W*, Bag A, Landis J, Zhan Y, Treff NR, Scott RT, Tao X, **Schindler K****, Xing J**. (2020). Exome sequencing links CEP120 mutation to maternally derived aneuploid risk conception. *Hum Reprod*. 35(9): 2134-48. PMC7828473 */** equal contribution

c. Vazquez BN, Blengini CS, Hernandez Y, Serrano L, **Schindler K**. (2019). SIRT7 promotes chromosome synapsis during prophase I of female meiosis. *Chromosoma*. 128(3): 369-83. PMC8494110

d. Blengini CS, Nguyen AL, Aboelenain M, **Schindler K**. (2021). Age-dependent integrity of the meiotic spindle assembly checkpoint in females requires Aurora kinase B. *Aging Cell*. 11: e13489. PMCID: PMC8590096

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2021	Ad Hoc member for Member Conflict: Topics in Endocrinology, Metabolism and Reproductive Biology study section, NIH
2021	Ad Hoc member for Nuclear and Cytoplasmic Structure/Function and Dynamics Study Section, NIH
2020- Present	Chair of Women in Reproductive Sciences committee for SSR
2020 - 2027	Director of Gametogenesis module, Marine Biological Laboratories/Frontiers in Reproduction, Woods Hole, MA
2020	Ad Hoc member for National Centers for Translational Research in Reproduction and Infertility (P50 Clinical Trial Optional) Review Panel, NIH
2020	Ad Hoc member for Member Conflict: Topics in Endocrinology, Metabolism and Reproductive Biology study section, NIH
2020	Ad Hoc member for Endocrinology, Metabolism, Nutrition and Reproductive Sciences Special Emphasis Panel, NIH
2020-Present	Associate Editor for Frontiers in Cell and Developmental Biology, Molecular and Cellular Reproduction section
2019-Present	Human Genetics Institute of NJ Imaging Core Faculty Director
2019	Ad hoc member of Reproduction, Andrology, and Gynecology Study Section, NIH
2019	Ad hoc member of NIH CSR study section assessing review integrity
2019	Ad Hoc member for Reproduction, Andrology and Gynecology Special Emphasis Panel

2018- Present	Associate Professor of Genetics, Rutgers University, Piscataway, NJ
2018- Present	Editorial board member, Molecular Reproduction and Development
2018	Member of search committee for NIH Center for Scientific Review Director, NIH
2017- Present	Associate Editor, Reproduction
2017	Ad hoc member of Cellular, Molecular, and Integrative Reproduction study section, NIH
2016	Ad hoc member of NIGMS Council meeting, NIH
2016	Ad hoc member of Molecular Genetics A study section, NIH
2012 - 2018	Assistant Professor of Genetics, Rutgers University, Piscataway, NJ
2012	National Academies Education Fellow in the Life Sciences, National Academies
2005 - 2011	Postdoctoral Fellow, University of Pennsylvania, Philadelphia, PA
1999 - 2005	Ph.D. Candidate, Thomas Jefferson University, Philadelphia, PA

Honors

2020	Excellence in Science Early Career Award, FASEB
2019	Faculty Scholar-Teacher Award, Rutgers University
2019	Distinguished Alumni Award, Frontiers in Reproduction
2019	Distinguished Alumni Award, Thomas Jefferson University
2018	Virendra B. Mahesh New Investigator Award, Society for the Study of Reproduction
2018	Board of Trustees Research Fellowship Award, Rutgers University
2018	Graduate Programs in Molecular Biosciences Directors' Early Career Award, Rutgers University School of Graduate Studies
2009	Pathways to Independence recipient (K99/R00), NIH
2009	Susan Heyner Award for excellence in postdoctoral research, University of Pennsylvania
2008	Lalor Foundation Merit Award, Lalor Foundation
2007	NRSA F32 Recipient, NIH
2007	Loan Repayment Program recipient for research in Contraception and Infertility, NIH
2005 - 2007	NRSA T32 Recipient, NIH/University of Pennsylvania
2003	NRSA T32 Predoctoral Recipient, NIH/Thomas Jefferson University
2002	Ralph Heimer Award for excellence in research and graduate studies, Thomas Jefferson University
1995 - 1996	Werner Kirsten NIH High School Intern, NIH

C. Contributions to Science

1. Establish that there are underlying genetic predispositions that contribute to increased aneuploid gamete production. Data from preimplantation genetic testing conducted at in vitro fertilization clinics indicate that although the incidence of embryo aneuploidy increases with maternal age, there are female patients that are phenotypically extreme. Because mistakes in female meiosis I are highly linked to aneuploid conception, we hypothesized that there are genetic variants that underlie some patients' elevated risk of producing aneuploid eggs. We first developed assays to use the mouse oocyte system as a meiotic system to assess biological significance of human genetic variants. We started with an evaluation of AURKB and AURKC as proof of principle (a-b), and are now identifying candidate genes and assessing their biological significance. (c) is our most recent publication from our unbiased approach where we sequenced the exomes of women who produce extreme numbers of aneuploid embryos and assess variants in centrosomes genes. (d) is a computational analysis of variants in non-coding regions of the genome associated female infertility. Many of these publications involve MPI Xing.

a. Nguyen AL, Marin D, Zhou A, Smoak EM, Gentilello AS, Cao Z, Fedick A, Wang Y, Taylor D, Scott Jr. RT, Xing J, Treff N, **Schindler K**. (2017). Identification and characterization of Aurora Kinase B and C variants associated with maternal aneuploidy. *Mol Hum Reprod*. 23(6): 406-16. PMID: 28369513

b. Fellmeth JE, Ghanaim EM, **Schindler K**. (2016). Characterization of macrozoospermia-associated AURKC mutations in a mammalian meiotic system. *Hum Mol Genet*. 25 (13): 2698-711. PMID: 27106102

c. Tyc KM*, El Yakoubi W*, Bag A, Landis J, Zhan Y, Treff NR, Scott RT, Tao X, **Schindler K****, Xing J**. (2020). Exome sequencing links CEP120 mutation to maternally derived aneuploid risk conception. *Hum Reprod*. 35(9): 2134-48. PMID: PMC7828473 */** equal contribution

d. Tyc KM, Wong A, Scott RT Jr, Tao X, **Schindler K,** Xing J. (2021). Analysis of DNA variants in miRNAs and miRNA 3'UTR binding sites in female infertility patients. *Lab Invest*. 101(4):503-512. PMID: PMC7987713

2. Identify chromosome-based factors correlated with age-dependent maternal gamete aneuploidy. A major question in the reproductive biology field is why are gametes from older women more prone to aneuploidy. In studies I conducted as a postdoctoral fellow, we discovered that the cohesins that hold sister chromatids together during meiosis I are degraded during the long life span of an oocyte, and not replenished (a). This hypothesis is one of the current leading models to explain the maternal age effect in oocytes. Recently, in my lab, we again became interested in reproductive aging. Using a mouse models of premature aging, we discovered that functions of Sirtuin 7 in DNA repair impinge on oocyte quality and aneuploidy by its requirement in meiotic prophase, and that Aurora kinase B inhibition of the other 2 Aurora homologs is required to protect euploidy with age (c-d).

a. Chiang T, Duncan FE, **Schindler K**, Schultz RM, Lampson MA. (2010). Weakened centromere cohesion is the primary cause of age-related aneuploidy in oocytes. *Curr Biol*. 20: 1522-8. PMID: PMC2939204

b. Vazquez BN, Blengini CS, Hernandez Y, Serrano L, **Schindler K**. (2019). SIRT7 promotes chromosome synapsis during prophase I of female meiosis. *Chromosoma*. 128(3): 369-83. PMID: PMC8494110

c. Aboelenain M and **Schindler K**. (2021). Aurora kinase B inhibits Aurora kinase A to control maternal mRNA translation in mouse oocytes. *Development*. 148(21): dev199560. PMID: 34636397

d. Blengini CS, Nguyen AL, Aboelenain M, **Schindler K**. (2021). Age-dependent integrity of the meiotic spindle assembly checkpoint in females requires Aurora kinase B. *Aging Cell*. 11: e13489. PMCID: PMC8590096

3. Discover Aurora kinase requirements during mammalian meiosis. The requirements for AURKB and AURKC during meiosis have been unclear because of a lack of gene- and protein-specific tools. As a postdoc, I led a project assessing oocytes from Aurora kinase C knockout mice to investigate unique AURKC functions and AURK compensatory abilities (a). I continued this line of inquiry in my own lab by generating mice that lacked both AURKB and AURKC in oocytes (b). We found that in knockouts, AURKA and AURKB compensate for loss of AURKC, that AURKC competes for binding chromosomes with AURKA, a strategy used to assist in spindle building, and that AURKB negatively regulates both AURKA and AURKC. The discovery that AURKA alone could support meiosis, led us to create oocyte-specific *Aurka* knockout mice where we found that AURKA is required to shape the meiotic spindle by inducing fragmentation of the spindle pole organizing centers (c). We were also interested if the AURKA compensatory pathway were conserved in male germ cells. We collaborated with Dr. Phil Jordan at Johns Hopkins to assess sperm-specific single and double knockouts (d) and found that the compensation is specific to females.

a. **Schindler K**, Davydenko O, Fram B, Lampson MA, Schultz RM. (2012). Maternally-recruited Aurora C kinase is more stable than Aurora B to support mouse oocyte maturation and early development. *PNAS.* 109(33): E2215-22. PMID: PMC3421190

b. Nguyen AL, Drutovic D, Vazquez B, El Yakoubi W, Gentilello AS, Malumbres M, Solc P, **Schindler K**. (2018). Genetic interactions between the Aurora kinases reveal new requirements for AURKB and AURKC during oocyte meiosis. *Current Biology*. 28(21): 3458-68. PMID: PMC6234855

c. Blengini CS, Ibrahimian P, Vaskovicova M, Drutovic D, Solc P, **Schindler K**. (2021). Aurora kinase A is essential for meiosis in mouse oocytes. *Plos Genet*. 17(4): e1009327. PMID: PMC8102010

d. Wellard SR, **Schindler K**, Jordan P. (2020). Aurora B and C kinases regulate prophase exit and chromosome segregation during spermatogenesis. *J. Cell Sci.* 133(23): jcs248831. PMCID: PMC7725601

4. Elucidate AURKC regulatory pathways in mouse oocytes. At metaphase I, the localization of the CPC is different than in mitosis because it not only localizes to centromere, but it localizes along the arms of the chromosomes in the bivalent. The localization of the Aurora kinase in the chromosomal passenger complex (CPC) is regulated by several mechanisms in mitosis, but nothing was known about its regulation in meiosis. We identified several epigenetic marks that regulate the timing and distribution of AURKC-CPC during meiosis I. These regulatory steps are important for AURKC-CPC function and protection of euploidy.

a. Balboula AZ, Blengini C, Gentilello AS, Takahasi M, **Schindler K**. (2017). Maternal RNA regulates Aurora C kinase during mouse oocyte maturation in a translation-independent fashion. *Biol Reprod*. 96(6): 1197-1209. PMID: PMC6279119

b. Quartuccio SM, Dipali SS, **Schindler K**. (2017). Haspin inhibition reveals functional differences of interchromatid axis-localized AURKB and AURKC. *Mol Biol Cell*. 8(17): 2233-2240. PMID: PMC5555651

c. Nguyen AL, Gentilello AS, Balboula AZ, Shrivastava V, Ohring J, **Schindler K**. (2014). Phosphorylation of threonine 3 on histone 3 by Haspin kinase is required for meiosis I in mouse oocytes. *J Cell Sci*. 127(23): 5066-78. PMID: PMC4248095

d. Balboula AZ, Stein P, Schultz RM, **Schindler K**. (2014). Knockdown of RBBP7 unveils a requirement of histone deacetylation for CPC function in mouse oocytes. *Cell Cycle*. 13(4): 600-11. PMID: PMC5896761

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/1Tgt6TGyRbaQFL/bibliography/public/