Final Progress Report for Research Projects Funded by Health Research Grants

Instructions: Please complete all of the items as instructed. Do not delete instructions. Do not leave any items blank; responses must be provided for all items. If your response to an item is "None", please specify "None" as your response. "Not applicable" is not an acceptable response for any of the items. There is no limit to the length of your response to any question. Responses should be single-spaced, no smaller than 12-point type. The report **must be completed using MS Word**. Submitted reports must be Word documents; they should not be converted to pdf format. Questions? Contact Health Research Program staff at 717-783-2548.

1. **Grantee Institution:** Magee-Womens Research Institute and Foundation

2. **Reporting Period (start and end date of grant award period):** 01/01/2010- 12/31/2010

3. **Grant Contact Person (First Name, M.I., Last Name, Degrees):** Cheryl A. Richards, MBA

4. **Grant Contact Person's Telephone Number:** 412-641-8932

5. **Grant SAP Number:** 4100050901

6. **Project Number and Title of Research Project:** 7 - The impact of age on the nematode germline

7. **Start and End Date of Research Project:** 01/01/2010- 12/31/2010

8. **Research Project Expenses**.

   9(A) Please provide the amount of health research grant funds spent on this project for the entire duration of the grant, including any interest earned that was spent:

   $ $707,099.00

   9(B) Provide the last names (include first initial if multiple individuals with the same last name are listed) of **all** persons who worked on this research project and were supported with health research funds. Include position titles (Principal Investigator, Graduate Assistant, Post-doctoral Fellow, etc.), percent of effort on project and total health research funds expended for the position. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name	Position Title	% of Effort on Project	Cost
Yanowitz	Assistant Professor	25%	$27,302.07
Kim	Student Intern	100%	$197.28
McGovern	Research Assistant	100%	$27,757.30

9(C) Provide the names of **all** persons who worked on this research project, but who *were not* supported with health research funds. Include position titles (Research Assistant, Administrative Assistant, etc.) and percent of effort on project. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name	Position Title	% of Effort on Project

9(D) Provide a list of **all** scientific equipment purchased as part of this research grant, a short description of the value (benefit) derived by the institution from this equipment, and the cost of the equipment.

Type of Scientific Equipment	Value Derived	Cost
Nikon A1 confocal	Establishment of Core Imaging Facility	$534,816.20
Volocity software	Part of Imaging Core	$28,416.50
Bond Max Immunostainer Module	High throughput immunohistochemistry tool, relevant to majority of the projects	$24,470

10. Co-funding of Research Project during Health Research Grant Award Period. Did this research project receive funding from any other source during the project period when it was supported by the health research grant?

Yes_____ No_____X____

If yes, please indicate the source and amount of other funds:

11. Leveraging of Additional Funds

11(A) As a result of the health research funds provided for this research project, were you able to apply for and/or obtain funding from other sources to continue or expand the research?

Yes_____ No_____X_____

If yes, please list the applications submitted (column A), the funding agency (National Institutes of Health—NIH, or other source in column B), the month and year when the application was submitted (column C), and the amount of funds requested (column D). If you have received a notice that the grant will be funded, please indicate the amount of funds to be awarded (column E). If the grant was not funded, insert "not funded" in column E.

Do not include funding from your own institution or from CURE (tobacco settlement funds). Do not include grants submitted prior to the start date of the grant as shown in Question 2. If you list grants submitted within 1-6 months of the start date of this grant, add a statement below the table indicating how the data/results from this project were used to secure that grant.

A. Title of research project on grant application	B. Funding agency (check those that apply)	C. Month and Year Submitted	D. Amount of funds requested:	E. Amount of funds to be awarded:
	☐NIH ☐ Other federal (specify:_____ _____) ☐ Nonfederal source (specify: _____)		$	$
	☐NIH ☐ Other federal (specify:_____ _____) ☐ Nonfederal source (specify: _____)		$	$
	☐NIH ☐ Other federal (specify:_____ _____) ☐ Nonfederal source (specify: _____)		$	$

11(B) Are you planning to apply for additional funding in the future to continue or expand the research?

Yes_____ No_____X_____

If yes, please describe your plans:

12. Future of Research Project. What are the future plans for this research project?

We have significantly increased our understanding of the factors that drive germline aging. Having a readout for differences in proliferative capacity, we now to better understand how this changes with age and whether we can identify the key regulators of this process.
We will use the infrastructure improvements to significantly advance our studies of genes required for meiotic crossover formation,

13. New Investigator Training and Development. Did students participate in project supported internships or graduate or post-graduate training for at least one semester or one summer?

Yes_____X__ No_____

If yes, how many students? Please specify in the tables below:

	Undergraduate	Masters	Pre-doc	Post-doc
Male				
Female	1		1	
Unknown				
Total	**1**		**1**	

	Undergraduate	Masters	Pre-doc	Post-doc
Hispanic				
Non-Hispanic	1		1	
Unknown				
Total	**1**		**1**	

	Undergraduate	Masters	Pre-doc	Post-doc
White			1	
Black				
Asian	1			
Other				
Unknown				
Total	**1**		**1**	

14. Recruitment of Out-of–State Researchers. Did you bring researchers into Pennsylvania to carry out this research project?

Yes_____ No___X_____

If yes, please list the name and degree of each researcher and his/her previous affiliation:

15. Impact on Research Capacity and Quality. Did the health research project enhance the quality and/or capacity of research at your institution?

Yes____X____ No_____

If yes, describe how improvements in infrastructure, the addition of new investigators, and other resources have led to more and better research.

The studies we conducted were made possible by a significant boon to our infrastructure provided by the purchase of a Nikon A1r confocal microscope and Volocity 3-D imaging software. The confocal was operational by June of 2010 and now serves as the key component of the core imaging facility at Magee-Womens Research Institute. The confocal microscope can be used for both fixed live cell imaging.

Forty-five individuals representing over twenty laboratories have been trained to use the microscope and imaging analysis software. The training sessions have fostered strong enthusiasm for the use of advanced imaging techniques for a broad range of studies including research into the etiology of breast cancer, pelvic floor dysfunction, meiosis, placental abnormalities, just to name a few. The ability to look deep within cells and in real-time will offers this department an unprecedented opportunity to advance our research that would not otherwise have been possible.

16. Collaboration, business and community involvement.

16(A) Did the health research funds lead to collaboration with research partners outside of your institution (e.g., entire university, entire hospital system)?

Yes_____ No____X_____

If yes, please describe the collaborations:

16(B) Did the research project result in commercial development of any research products?

Yes_____ No____X_____

If yes, please describe commercial development activities that resulted from the research project:

16(C) Did the research lead to new involvement with the community?

Yes_____ No_____X____

If yes, please describe involvement with community groups that resulted from the research project:

17. Progress in Achieving Research Goals, Objectives and Aims.

List the project goals, objectives and specific aims (as contained in the grant application's strategic plan). Summarize the progress made in achieving these goals, objectives and aims for the entire grant award period. Indicate whether or not each goal/objective/aim was achieved; if something was not achieved, note the reasons why. Describe the methods used. If changes were made to the research goals/objectives/aims, methods, design or timeline since the original grant application was submitted, please describe the changes. Provide detailed results of the project. Include evidence of the data that was generated and analyzed, and provide tables, graphs, and figures of the data. List published abstracts, poster presentations and scientific meeting presentations at the end of the summary of progress; peer-reviewed publications should be listed under item 20.

This response should be a DETAILED report of the methods and findings. It is not sufficient to state that the work was completed. Insufficient information may result in an unfavorable performance review, which may jeopardize future funding. If research findings are pending publication you must still include enough detail for the expert peer reviewers to evaluate the progress during the course of the project.

Health research grants funded under the Tobacco Settlement Act will be evaluated via a performance review by an expert panel of researchers and clinicians who will assess project work using this Final Progress Report, all project Annual Reports and the project's strategic plan. After the final performance review of each project is complete, approximately 12-16 months after the end of the grant, this Final Progress Report, as well as the Final Performance Review Report containing the comments of the expert review panel, and the grantee's written response to the Final Performance Review Report, will be posted on the CURE Web site.

There is no limit to the length of your response. Responses must be single-spaced below, no smaller than 12-point type. If you cut and paste text from a publication, be sure symbols print properly, e.g., the Greek symbol for alpha (α) and beta (ß) should not print as boxes (□) and include the appropriate citation(s). DO NOT DELETE THESE INSTRUCTIONS.

Defects in chromosome segregation during meiosis are a leading cause of miscarriage and birth defects due to upsets in chromosomal content. As women delay having children into their thirties and forties, they face a huge increase in the risk of having a baby with a chromosomal abnormality resulting from a meiotic failure. Thus, understanding the etiology of reproductive decline and associated chromosomal abnormalites is of critical importance to human fertility research.

During meiosis, chromosomes undergo vast rearrangements that ultimately allow for the exchange of genetic material between maternal and paternal chromosomes, known as meiotic crossover recombination. To facilitate recombination, the chromosome axis is configured to prevent exchanges between sister chromosomes and promote exchange between homologues. Homologous attachments are reinforced by the synaptonemal complex, a protein bridge that forms along the length of the aligned homologues. After crossover exchange, chromosomes partially disassemble the SC, condense, and reorganize in preparation for the first meiotic division. In addition to the events of meiosis, oocytes grow substantially and produce vast reservoirs of RNA and protein that the embryo will require during its early stages of development. Thus, during early oocyte development, chromosome organization needs to take into account the requirement for high transcriptional activity and meiotic crossover recombination.

We hypothesized that higher order DNA structure would be a major determinant of germline aging, and that changes in histone post-transcriptional modifications (HPTMs) and histone variants would be apparent in aged germlines. To explore this hypothesis, we proposed to determine whether the expression and localization of HPTM and histone variants differed in young and old germline tissue (Aim 1) and to determine whether any such differences were controlled by the pathways that control somatic aging (Aim 2).

To be able to perform these experiments, we first optimized conditions for fixation of old *C. elegans* germlines. We found that although aged worms were generally more sensitive to manipulation and many animals died during the course of the 9 day experiments, those animals that survived were amenable to dissection and their germlines were no more sensitive to fixation that young animals. Therefore, we relied on standard fixation protocols: 1% paraformaldehyde, freeze cracking and 1 minute in ethanol. However, if antibodies did not give stain, different staining conditions were tested: 3% PFA +/- ethanol treatment; replacing ethanol with methanol, pure methanol fixation, or methanol/ acetone fixation. Surprisingly, we found that in no case did changing the fixation procedure increase staining efficiency.

The complete set of antibodies that we tested is listed in Table 1. Germlines from adult hermaphrodites ages t= 1, 5, and 9 days old were dissected, fixed and stained for each of the antibodies. Z stacks of gonads were collected using the Nikon A1r confocal microscope which was purchased with funds from this grant. We took 0.2um thick stacks through the entire thickness of the gonadal tissue. 3-D reconstructions of germlines were analyzed using Volocity imaging software (Perkin Elmer Corp, USA).

Germline staining of histone post-translational modifications was evaluated using a number of qualitative parameters. We examined the overall pattern of each modification within germline

tissue; the nuclear-specific localization in different regions of the germline, and the overall intensity. A sampling of the images we attained are shown in Figure 1. With one exception (discussed below), we saw no differences in HPTM staining between young and old germline tissues. In both young and old germline tissue, a number of the modifications differentially localize to autosomes and are excluded from binding on the X chromosomes (for example, H4K12Ac, Figure 1) or vice versa. These localization patterns reflect differences in the transcriptional status of the X and autosomes: during the majority of meiotic development, the X is transcriptionally repressed. Our observation that histone modifications associated with transcriptional activity and silencing are unchanged in the aging germline strongly suggests that reproductive senescence does not arise from defects in silencing of the X chromosome.

The only reproducible difference in HPTM distribution that we observed was a change in the number of nuclei that stain for phosphorylated histone H3 on Serine 10 (H3Ser10Ph). The reduction from an average of ~7 positive nuclei to fewer than 1 H3Ser10Ph positive nucleus per proliferative zone correlates with onset of reproductive senescence. Analysis of mutants defective in two somatic aging pathways, the insulin signaling pathway or the *sir-2* pathway did not increase reproductive lifespan in our laboratory, suggesting that these pathways are like not influencing proliferative capacity of the germline stem cell population.

The results of our efforts have led us to a better understanding of the changes that occur during aging within the germline. Although we hypothesized that epigenetic changes would drive force reproductive aging, our results to date suggest otherwise. However, these experiments did not exhaustively test all histone modifications. Therefore it remains possible that modifications or variants that we did not examine due to technical reasons (or lack of functional antibodies) actually change during reproductive. Alternatively, it may be that immuno-staining was insufficiently sensitive to detect functional differences in critical modifications. In favor of this interpretation, it has been shown that mutations in the histone demethylase, *spr-5*, prevent the resetting of this mark each generation allow for the gradual build up this modification in the mutant animals and eventual sterility. In these animals, from one generation to the next, a change in methylation status cannot be detected. However, over many generations, these changes become readily apparent.

Therefore, we have developed an assay for accumulated changes in the epigenetic landscape. By maintaining lines bred from the oldest and youngest mothers, we could determine whether there is a decline in reproductive fitness in the aged maternal germline. We initiated these studies with the analysis of two mutant backgrounds that our lab had established showed a loss of fecundity over many (30-50) generations. RFS-1 is a DNA repair protein required to promote replication fork progression. XND-1 is a meiotic chromatin-associated protein that regulates histone H2A lysine 5 acetylation. By carrying mutations in these genes through the aged maternal germline, we could observe dramatic differences in reproductive capacity after only 5 generations. In the case of *rfs-1*, when carried through young mothers, no evidence of sterility was apparent at generation 5; whereas ~80% of the animals showed decrease fecundity when passaged through the aged germline. For *xnd-1*, in young animals 40% of the population is sterile due to defects in oocytes development. This is exacerbated to >95% sterility when maintained in the old maternal germline. These experiments provide a proof of principle for genetic analysis of epigenetic changes during reproductive aging and set the stage for future studies.

Table 1. Histone Post-Translation Modifications Analyzed

Antibody	Company		Antibody	Company		Antibody	Company
H2A K5Ac	CS, Upstate		H3K9Ac	CS		H3K56Ac	Upstate
H2B K5Ac	CS		H3Ser10Ph	CS		H4K8Ac	Abcam
H3K4me2	Upstate		H3K18Ac	Abcam		H4K12Ac	Abcam
H3K4me3	Lake Placid		H3K23Ac	Abcam		H4K16Ac	Upstate
H3K9me2	Upstate		H3K27me3	Lake Placid		H4pentaAc	Lake Placid
H3K9me3	Abcam		H4K5Ac	Millipore		Htz-1	Csankovski lab

CS= Cell Signaling,

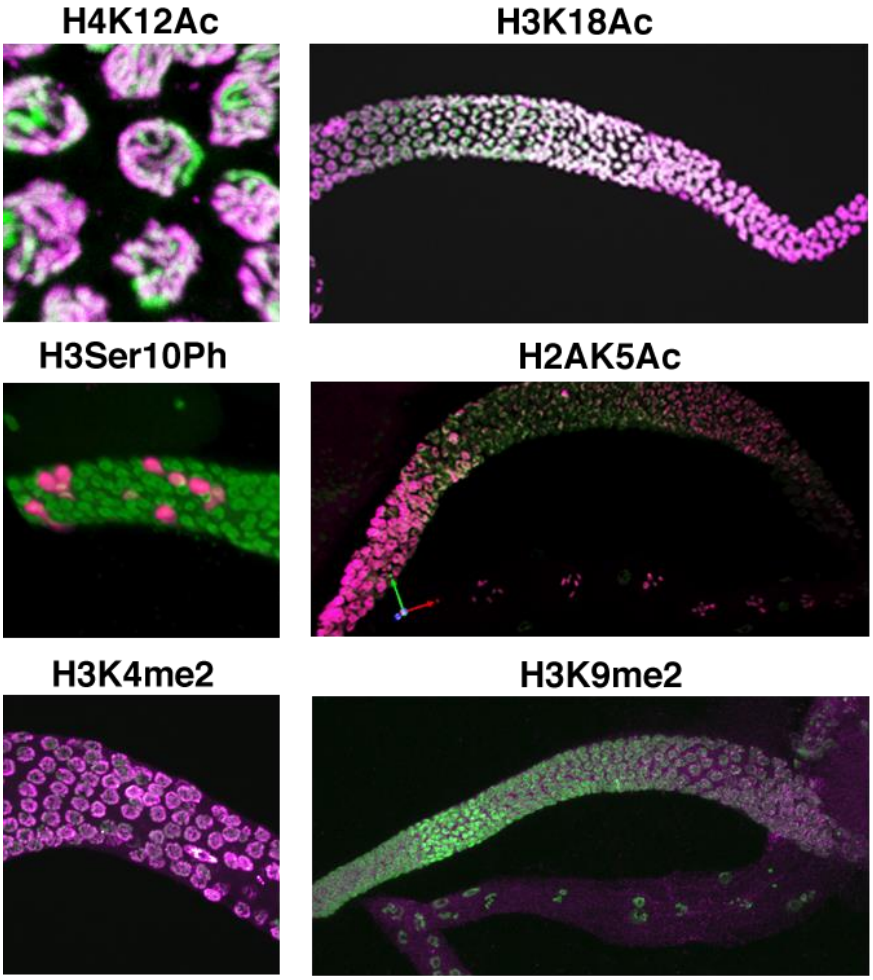

Figure 1. Representative antibody localization patterns for histone post-translational modification in *C. elegans* germline tissues. Close-ups on left show specific staining in subsets of nuclei or sub-nuclear domains. Full gonads on right panels show different distributions along the distal-proximal axis. DNA, green; antibody, magenta.

18. Extent of Clinical Activities Initiated and Completed. Items 18(A) and 18(B) should be completed for all research projects. If the project was restricted to secondary analysis of clinical data or data analysis of clinical research, then responses to 18(A) and 18(B) should be "No."

18(A) Did you initiate a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

_____Yes
__X___No

18(B) Did you complete a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

_____Yes
___X__No

If "Yes" to either 18(A) or 18(B), items 18(C) – (F) must also be completed. (Do NOT complete 18(C-F) if 18(A) and 18(B) are both "No.")

18(C) How many hospital and health care professionals were involved in the research project?

_____Number of hospital and health care professionals involved in the research project

18(D) How many subjects were included in the study compared to targeted goals?

_____Number of subjects originally targeted to be included in the study
_____Number of subjects enrolled in the study

18(E) How many subjects were enrolled in the study by gender, ethnicity and race?

Gender:
_____Males
_____Females
_____Unknown

Ethnicity:
_____Latinos or Hispanics
_____Not Latinos or Hispanics
_____Unknown

Race:
_____American Indian or Alaska Native
_____Asian
_____Blacks or African American

_____Native Hawaiian or Other Pacific Islander
_____White
_____Other, specify:_____
_____Unknown

18(F) Where was the research study conducted? (List the county where the research study was conducted. If the treatment, prevention and diagnostic tests were offered in more than one county, list all of the counties where the research study was conducted.)

19. Human Embryonic Stem Cell Research. Item 19(A) should be completed for all research projects. If the research project involved human embryonic stem cells, items 19(B) and 19(C) must also be completed.

19(A) Did this project involve, in any capacity, human embryonic stem cells?
_____Yes
___X__ No

19(B) Were these stem cell lines NIH-approved lines that were derived outside of Pennsylvania?
_____Yes
_____ No

19(C) Please describe how this project involved human embryonic stem cells:

20. Articles Submitted to Peer-Reviewed Publications.

20(A) Identify all publications that resulted from the research performed during the funding period and that have been submitted to peer-reviewed publications. Do not list journal abstracts or presentations at professional meetings; abstract and meeting presentations should be listed at the end of item 17. **Include only those publications that acknowledge the Pennsylvania Department of Health as a funding source** (as required in the grant agreement). List the title of the journal article, the authors, the name of the peer-reviewed publication, the month and year when it was submitted, and the status of publication (submitted for publication, accepted for publication or published.). Submit an electronic copy of each publication, listed in the table, in a PDF version 5.0.5 format, 1,200 dpi. Filenames for each publication should include the number of the research project, the last name of the PI, the number of the publication and an abbreviated research project title. For example, if you submit two publications for PI Smith for the "Cognition and MRI in Older Adults" research project (Project 1), and two publications for PI Zhang for the "Lung Cancer" research project (Project 3), the filenames should be:

Project 1 – Smith – Publication 1 – Cognition and MRI
Project 1 – Smith – Publication 2 – Cognition and MRI
Project 3 – Zhang – Publication 1 – Lung Cancer

Project 3 – Zhang – Publication 2 – Lung Cancer

If the publication is not available electronically, provide 5 paper copies of the publication.

Note: The grant agreement requires that recipients acknowledge the Pennsylvania Department of Health funding in all publications. Please ensure that all publications listed acknowledge the Department of Health funding. If a publication does not acknowledge the funding from the Commonwealth, do not list the publication.

Title of Journal Article:	Authors:	Name of Peer-reviewed Publication:	Month and Year Submitted:	Publication Status (check appropriate box below):
1.				☐Submitted ☐Accepted ☐Published
2.				☐Submitted ☐Accepted ☐Published
3.				☐Submitted ☐Accepted ☐Published

20(B) Based on this project, are you planning to submit articles to peer-reviewed publications in the future?

Yes_____ No____X___

If yes, please describe your plans:

21. Changes in Outcome, Impact and Effectiveness Attributable to the Research Project. Describe the outcome, impact, and effectiveness of the research project by summarizing its impact on the incidence of disease, death from disease, stage of disease at time of diagnosis, or other relevant measures of outcome, impact or effectiveness of the research project. If there were no changes, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

None

22. Major Discoveries, New Drugs, and New Approaches for Prevention Diagnosis and Treatment. Describe major discoveries, new drugs, and new approaches for prevention, diagnosis and treatment that are attributable to the completed research project. If there were no major discoveries, drugs or approaches, insert "None"; do not use "Not applicable."

Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

None

23. Inventions, Patents and Commercial Development Opportunities.

23(A) Were any inventions, which may be patentable or otherwise protectable under Title 35 of the United States Code, conceived or first actually reduced to practice in the performance of work under this health research grant? Yes_____ No___X_____

If "Yes" to 23(A), complete items a – g below for each invention. (Do NOT complete items a - g if 23(A) is "No.")

a. Title of Invention:

b. Name of Inventor(s):

c. Technical Description of Invention (describe nature, purpose, operation and physical, chemical, biological or electrical characteristics of the invention):

d. Was a patent filed for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No___

If yes, indicate date patent was filed:

e. Was a patent issued for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No___
If yes, indicate number of patent, title and date issued:
Patent number:
Title of patent:
Date issued:

f. Were any licenses granted for the patent obtained as a result of work performed under this health research grant? Yes_____ No___

If yes, how many licenses were granted?_____

g. Were any commercial development activities taken to develop the invention into a commercial product or service for manufacture or sale? Yes_____ No___

If yes, describe the commercial development activities:

23(B) Based on the results of this project, are you planning to file for any licenses or patents, or undertake any commercial development opportunities in the future?

Yes_____ No_____X_____

If yes, please describe your plans:

24. Key Investigator Qualifications. Briefly describe the education, research interests and experience and professional commitments of the Principal Investigator and all other key investigators. In place of narrative you may insert the NIH biosketch form here; however, please limit each biosketch to 1-2 pages. *For Nonformula grants only – include information for only those key investigators whose biosketches were not included in the original grant application.*

BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Judith Yanowitz	Assistant Professor
eRA COMMONS USER NAME (credential, e.g., agency login)	
yanowitz	

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Massachusetts Institute of Technology, Cambridge, MA	B.S.	1991	Biology
Princeton University, Princeton, NJ	Ph.D.	1999	Molecular Biology
Carnegie Institution for Science, Baltimore, MD	Postdoctoral	2003	Genetics

A. Personal Statement

My research is aimed at understanding how higher order DNA structure affects the critical process of meiotic crossover (CO) recombination and reproductive aging. CO formation is highly regulated to ensure that each chromosome gets a CO, that COs are distributed along the chromosome, and that they are well positioned for distribution. Defects in this process are a leading cause of infertility and are known to increase with maternal age. I have been using *C. elegans* as a model system for over ten years and have gathered the tools and knowledge of the field that are necessary to make this project successful. My network of colleagues in the worm and meiosis communities bring additional strength to my research plan by providing specific technical know-how and provision of reagents, as well as an exchange of ideas. Over the last seven years, I have run a small lab consisting primarily of undergraduate researchers many of whom are now at leading graduate schools across the country. Through these experiences, I have learned valuable mentoring and leadership skills that will allow me

to productively administer these projects. In summary, I have demonstrated my capacity to develop and build a research program in an area of research that is relevant to human reproduction.

B. Positions and Honors

Positions and Employment

1991 – 1993	Research Technician, Rockefeller University, New York, NY
1993 - 1999	Graduate Research Assistant, Department of Molecular Biology, Princeton University, Princeton, NJ
Fall 1998	Adjunct Faculty, Department of Biology, Rider University, Lawrenceville, NJ
1999 - 2003	Postdoctoral Fellow, Department of Embryology, Carnegie Institution for Science, Baltimore, MD
2003 - 2009	Staff Associate, Department of Embryology, Carnegie Institution for Science, Baltimore, MD
2009 - 2010	Visiting Assistant Professor, Magee-Womens Research Institute and Department of Obstetrics, Gynecology and Reproductive Sciences, University of Pittsburgh School of Medicine, Pittsburgh, PA
2010 - Present	Assistant Professor, Magee-Womens Research Institute and Department of Obstetrics, Gynecology and Reproductive Sciences, University of Pittsburgh School of Medicine, Pittsburgh, PA

Honors

2000 – 2003	NIH/NRSA Postdoctoral Fellowship

Other Experience and Professional Membership

1994 - present	Member, Association for Women in Science
1995 - present	Member, Genetics Society of America
1998 – 2009	Member, Society for Developmental Biology
1999 - present	Member, Sigma Xi
2000 - present	Member, New York Academy of Sciences
2007 – 2008	Member, American Society for Cell Biology

C. Selected Publications

Most Relevant to the Current Application

1. Yanowitz, J. (2010). Meiosis: Making a break for it. Curr. Opin. Cell Biol. 22(6):744-51.
2. Wagner, C.R., Kuervers, L., Baillie, D.L., and Yanowitz, J. (2010). *xnd-1* regulates the global recombination landscape in *C.elegans*. Nature 467(7317):839-43.
3. Lim, J.G., Stine, R.R., and Yanowitz, J. (2008). Domain-specific regulation of recombination in *C. elegans* in response to temperature age, and sex. Genetics, 180(2): 715-26.
4. Yanowitz, J. (2008). Genome integrity is regulated by the *C. elegans* Rad51D homolog, *rfs-1*. Genetics, 179(1): 249-62.

5. Ward, J.D., Barber, L.J., Petalcorin, M.I.R., Yanowitz, J., and Boulton, S.J. (2007). Replication blocking lesions present a unique substrate for homologous recombination. Embo J., 26(14): 3384-96.

D. Research Support

Ongoing Research Support

K01AG031296 04/01/2010 – 02/28/2013

Aging and Meiosis in the Nematode Germline

The goal of this project is to develop *C. elegans* as a model system for reproductive aging and determine if know aging pathways play a role in this process.

Role: PI