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:** The Institute for Cancer Research

2. **Reporting Period (start and end date of grant award period):** 1/1/2012 – 6/30/2014

3. **Grant Contact Person (First Name, M.I., Last Name, Degrees):** Maria Minko Gill

4. **Grant Contact Person's Telephone Number:** 215-728-2659

5. **Grant SAP Number:** 4100057660

6. **Project Number and Title of Research Project:** 04-Characterization of Novel Epigenetic Factors

7. **Start and End Date of Research Project:** 1/1/2012 – 6/30/2014

8. **Name of Principal Investigator for the Research Project:** Richard Katz, Ph.D.

9. **Research Project Expenses**.

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

   $ 496,002

   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, First Name	Position Title	% of Effort on Project	Cost
Katz, Richard	PI	30% years 1-2	$82,458.01
Merkel, George	Scientific Assistant	60% years 1-2	$81,273.86
Poleshko, Andrey	Postdoctoral Associate	100% years 1, 40% year 2	$62,313.63
Shubina, Maria	Graduate Student	100% year 1	$17,198.52
Mansfield, Katelyn	Student Assistant	100% year 2	$1,550.17
Miller, Matthew	Summer Assistant	100% year 1	$1,531.68
Dunlevy, Kelly	Summer Assistant	100% year 2	$4,976.68

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, First Name	Position Title	% of Effort on Project
None		

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
None		

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___X___ No_____

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 awarded:
R01 - Heterochromatin-Nuclear Lamina Attachments and Dynamics	☒ NIH ☐ Other federal (specify:_____) ☐ Nonfederal source (specify:_)	Feb 2014	$2,231,250	Not funded

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

Yes__X___ No_____

If yes, please describe your plans:

A revised NIH application will be submitted.

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

Future plans include publishing additional findings, and applying for NIH funding. New preliminary results suggest a link between PRR14 expression and breast cancer. These findings will provide highly relevant, additional avenues of study. We will also continue to study the basic cell biological processes related to tethering of heterochromatin to the nuclear lamina.

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	1			1
Female	2		1	
Unknown				
Total	**3**		**1**	**1**

	Undergraduate	Masters	Pre-doc	Post-doc
Hispanic				
Non-Hispanic	3		1	1
Unknown				
Total	**3**		**1**	**1**

	Undergraduate	Masters	Pre-doc	Post-doc
White	3		1	1
Black				
Asian				
Other				
Unknown				
Total	**3**		**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.

This Health Research Grant provided critical funding for research, which was essential for our work and greatly benefited our Center.

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 agreement). Summarize the progress made in achieving these goals, objectives and aims for the period that the project was funded (i.e., from project start date through end date). 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.

Specific Aims

Aim 1. To characterize novel human proteins that were identified in a genome-wide functional screen for factors that control epigenetic gene silencing.

Aim 2. To determine the role of sumoylation, and SUMO (small ubiquitin-like modifier) enzyme networks in global epigenetic gene silencing.

Our work has focused on Aim 1 of the proposal, to determine the detailed role of the previously uncharacterized human protein initially denoted "Mammalian Genome Collection A" (MGCA), now denoted by the gene name Proline Rich 14 (PRR14). Our preliminary studies had shown that the PRR14 protein localizes to the nuclear lamina and that knockdown of PRR14 interrupts epigenetic gene silencing, and produces nuclear distortions similar to that observed in human nuclear lamina diseases and cancer. We have now shown that PRR14 functions to attach heterochromatin to the nuclear lamina. Work described in this Final Report has now been published (see Question 20).

A conserved organizational feature of eukaryotic nuclei is the peripheral heterochromatin compartment, which provides a protected area for epigenetically silent genes and gene-poor DNA. In metazoan cells this compartment is associated with the nuclear lamina, the protein meshwork at the inner edge of the nucleus. Heterochromatin-nuclear lamina interactions promote epigenetic gene silencing. Important biological roles for the nuclear lamina as a docking site for peripheral heterochromatin continue to emerge within many normal and disease processes, including development, cancer, aging, and cell senescence. In particular, it will be important to explore nuclear lamina-heterochromatin "tethering" mechanisms in normal and diseased cells, as differential interactions may affect gene expression and thereby underlie human disease. In view of the broad biological impact of nuclear lamina-heterochromatin attachment, it is critical to obtain a comprehensive view of the attachment mechanisms. Below we provide a summary of work carried out during the funding period that has addressed the mechanisms of PRR14-mediated heterochromatin tethering.

In the first Annual Report, we described our initial characterization of PRR14. The experiments investigated: the role of PRR14 in control of gene expression, the domain structure of PRR14, and the mechanism by which PRR14 attaches to the nuclear lamina. In the second Annual Report, we described the mitotic behavior of PRR14. We proposed that it serves a novel function in specifying heterochromatin for post-mitotic reassembly at the nuclear lamina. We

also investigated in detail the mechanism by which PRR14 binds to heterochromatin through HP1. We found that there is an HP1-binding motif at the N-terminus of PRR14. Furthermore we showed colocalization of PRR14 with HP1, and that localization of PRR14 was dependent on HP1. Our overall findings relied heavily on imaging, and during the second and third reporting periods we needed to develop quantitative methods of image analysis. In particular, we were able to quantitate the release of PRR14 from the nuclear lamina after knockdown of lamina components, as well as quantitate the release of heterochromatin from the nuclear lamina after PRR14 knockdown. In the third Annual Report we describe our final published results. We also report on several experiments to refine our understanding of how PRR14 interacts with the nuclear lamina. Fine mapping of the PRR14 nuclear lamina binding site was carried out. We also used imaging software to create 3D-renderings of PRR14 behavior during mitosis to reveal additional details. Below we provide an overview of the completed Aim 1 project and a detailed summary of the published findings.

The nuclear lamina is a meshwork composed of intermediate filament proteins, the A- and B-type lamins: Lamin A/C, Lamin B1, and Lamin B2. The N-terminal domain of PRR14 binds to Heterochromatin Protein 1 (HP1), which is in turn bound to H3K9me3-modifed heterochromatin. The bivalent tethering function of PRR14 is facilitated by a second domain that interacts with the Lamin A/C component of the nuclear lamina (Figure 1, and see below). Furthermore, we found that PRR14 disassembles and reassembles in a specific manner during mitosis, first binding to heterochromatin in anaphase, before reattaching to the assembling nuclear lamina (Figure 2). Our model predicts that PRR14 thereby provides a mechanism to specify heterochromatin for reattachment at the nuclear lamina. In order to study the dynamics of PRR14 during mitosis, we processed confocal images to produce 3D-rendering (Figure 3). This has allowed us to study specific defects in nuclear lamina-heterochromatin reassembly after PRR14-based siRNA knockdown (data not shown).

Figure 4 shows a summary of our detailed mapping studies of PRR14 functional domains. Using confocal imaging, we found that that the PRR14 N-terminus binds to heterochromatin and central region is required for nuclear lamina association. The binding of the PRR14 to HP1 was demonstrated by mutating the HP1 consensus binding sequence at the PRR14 N-terminus. The V54E,V55E mutant in the context of the N-terminal 1-135 fragment fails to localize to heterochromatin (data not shown). To further confirm that the 1-135 fragment was binding to HP1/heterochromatin, an HP1 siRNA knockdown experiment was carried out. As shown in Figure 5, knockdown of HP1 resulted in the release of the N-terminal 1-135 fragment from heterochromatin. Fine mapping studies on the nuclear lamina binding site of PRR14 have also been carried out (data not shown).

To confirm the binding of full length PRR14 to heterochromatin, we designed the following experiment. Full length PRR14 localizes to the nuclear lamina during interphase and attaches to neighboring peripheral heterochromatin through HP1 (Figures 1 and 2). The nuclear lamina is disassembled during early mitosis, releasing PRR14 (Figures 2 and 3). PRR14 is also released from HP1/heterochromatin. HP1 is known to be displaced from heterochromatin early in mitosis through the activity of Aurora B kinase. It was therefore predicted that inhibition of Aurora B would result in heterochromatin retention of both HP1 and PRR14. As shown in Figure 6, treatment with the Aurora B kinase inhibitor ZM447439 resulted in retention of HP1 on

chromatin in early mitosis, and PRR14 colocalized with HP1. To ask whether such localization of PRR14 was HP1-dependent, siRNA knockdown of HP1 isoforms was carried out in conjunction with inhibitor treatment. As shown in Figure 6, knockdown of all three HP1 isoforms resulted in loss of PRR14 heterochromatin binding.

To further address how PRR14 localizes to the nuclear lamina in interphase, siRNA knockdown of individual nuclear lamina components was carried out, and the effect on localization of GFP-tagged PRR14 was monitored by confocal microscopy. As shown in Figure 7, siRNA knockdown of Lamin A/C promoted release of PRR14 from the nuclear periphery.

Having established that PRR14 attaches to both HP1-marked heterochromatin and the nuclear lamina, the proposed tethering function was tested in detail. Shown in Figures 8 and 9 are experiments that address the comparative roles of Lamin A/C, LBR (another proposed heterochromatin tether), and PRR14 in maintaining the peripheral heterochromatin compartment. These three proteins were knocked down using siRNA, and the effects on positioning of H3K9me3-marked peripheral heterochromatin were measured using image analysis. As shown in Figure 8, PRR14 knockdown uniquely promoted release of heterochromatin from the nuclear periphery. Only combined knockdown of LBR and LaminA/C produced a similar effect. Image analysis depicting the effect of PRR14 knockdown on peripheral heterochromatin is shown in Figure 9.

As noted, we have worked mainly on Aim 1 of the project. The work led us to a major discovery, and we focused the resources in this area. We feel that this focus was highly justified. Aim 2 continues to be of interest, and we plan work on this project in the future.

In summary, we performed detailed mechanistic studies that have provided new and important insights into the organization of chromatin in human cells.

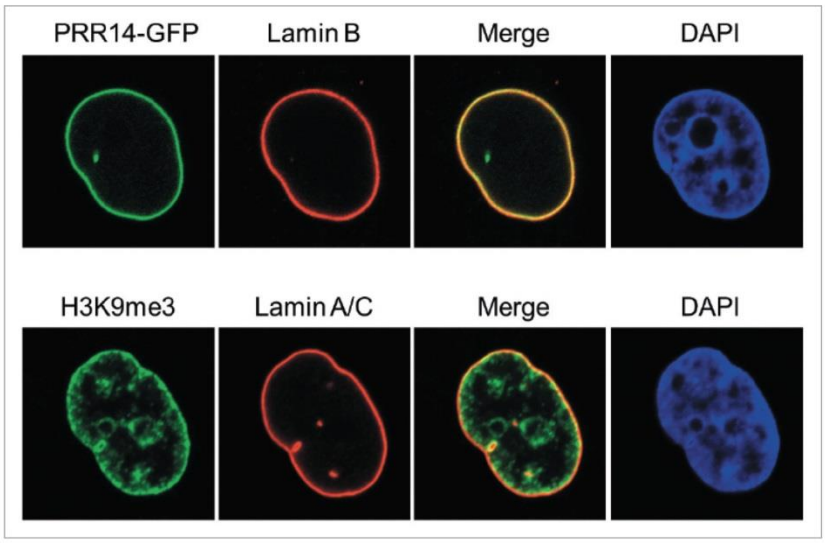

Figure 1. Localization of PRR14 in association with H3K9me3-marked heterochromatin at the nuclear periphery.

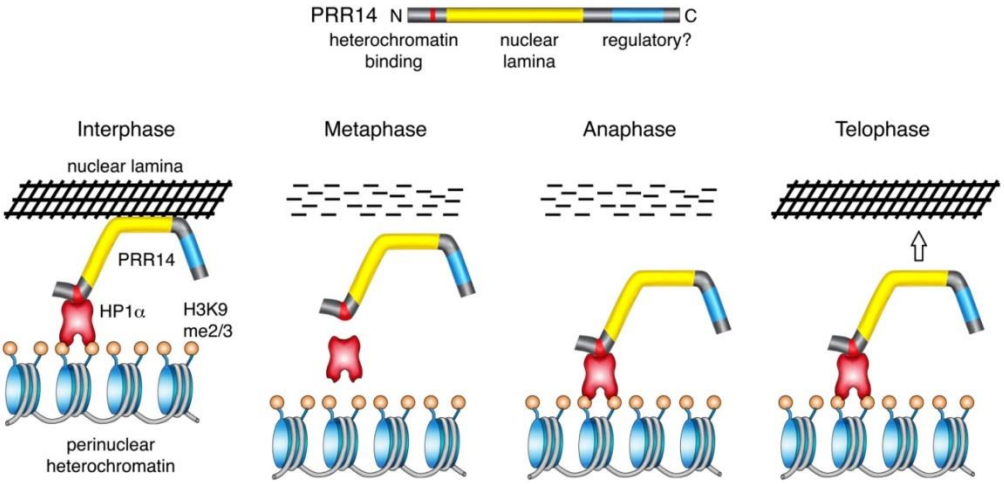

Figure 2. Model for role of PRR14 in the tethering of heterochromatin at the nuclear lamina. Depicted are PRR14-mediated attachment of HP1-H3k9me3-marked heterochromatin to the nuclear lamina, and the disassembly and reassembly steps that occur during mitosis.

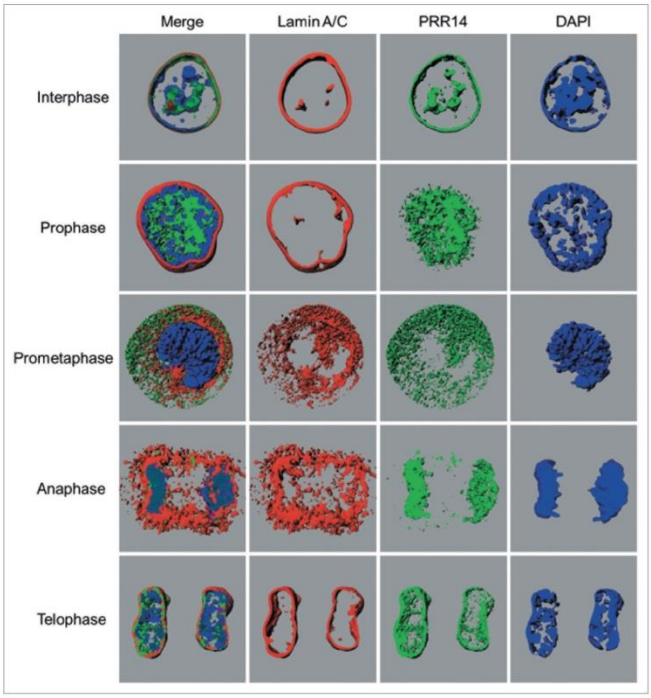

Figure 3. Three-dimensional renderings of confocal images showing disassembly and reassembly of PRR14 during mitosis, in relation to the nuclear lamina component Lamin A/C (red) and chromatin (blue).

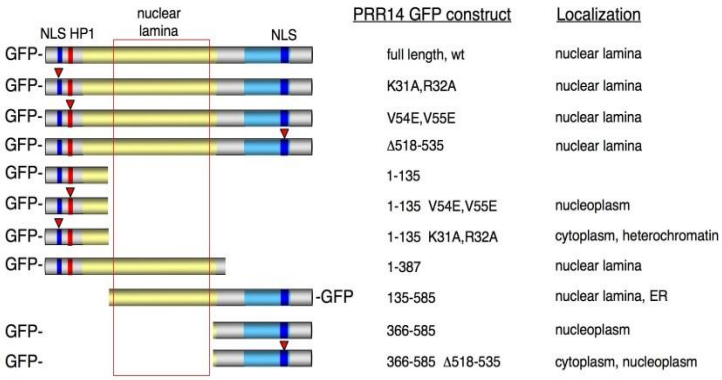

Figure 4. Mapping of PRR14 HP1/heterochromatin and nuclear lamina binding sites. Mapping was carried out using GFP-tagged proteins and confocal microscopy.

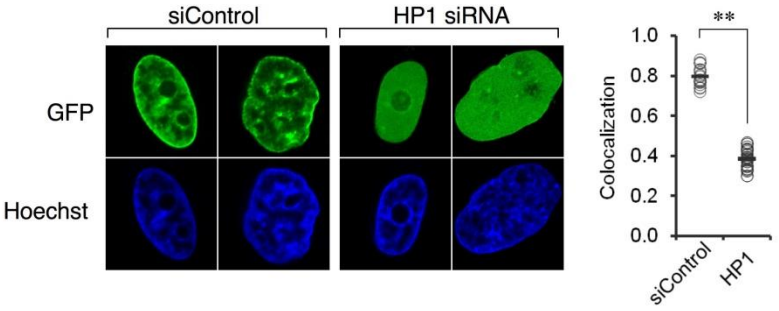

Figure 5. Binding of the PRR14 N-terminal 1-135 domain to heterochromatin is dependent on HP1. HP1 siRNA knockdown results in relocalization of PRR14 to the nucleoplasm.

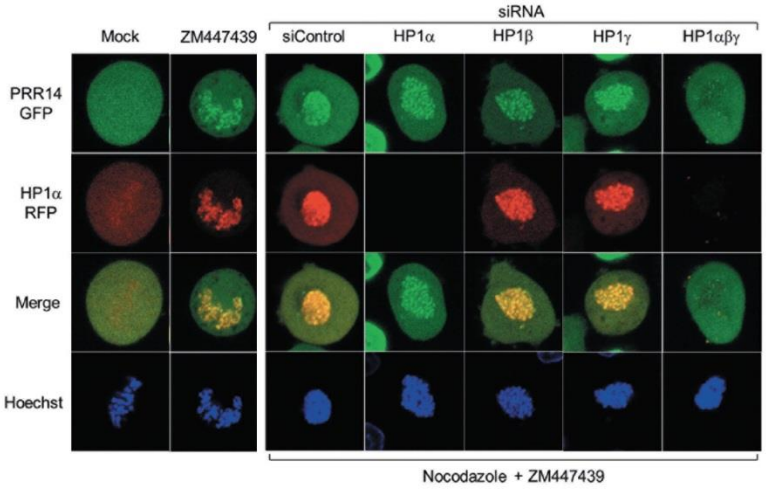

Figure 6. PRR14 and HP1 colocalize on heterochromatin, and PR114 localization is dependent on HP1.

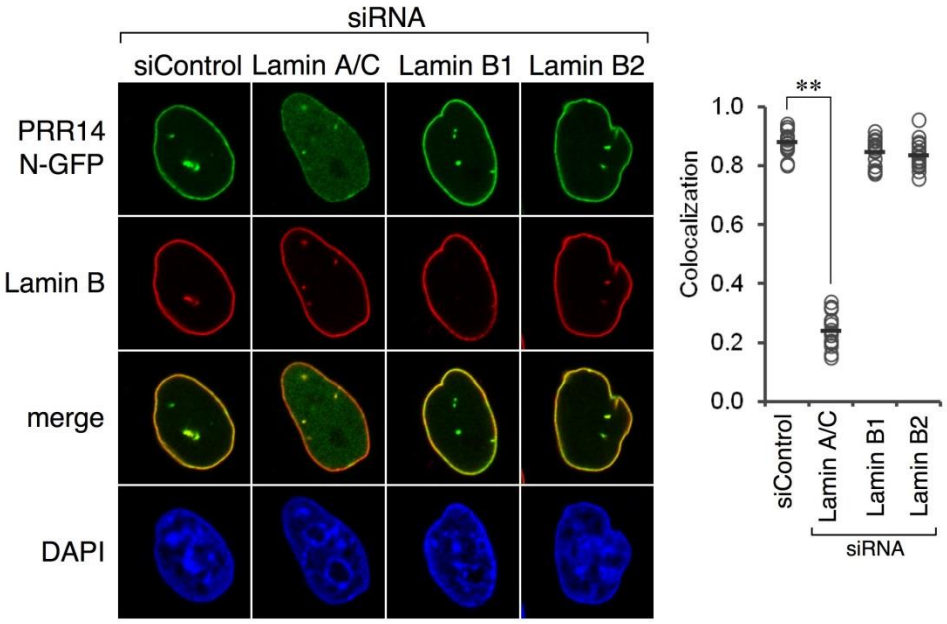

Figure 7. Lamin A/C is required for PRR14 localization to the nuclear periphery. SiRNA knockdown of lamin A/C results relocalization of PRR14 to the nuclear periphery. Image quantitation is shown at right.

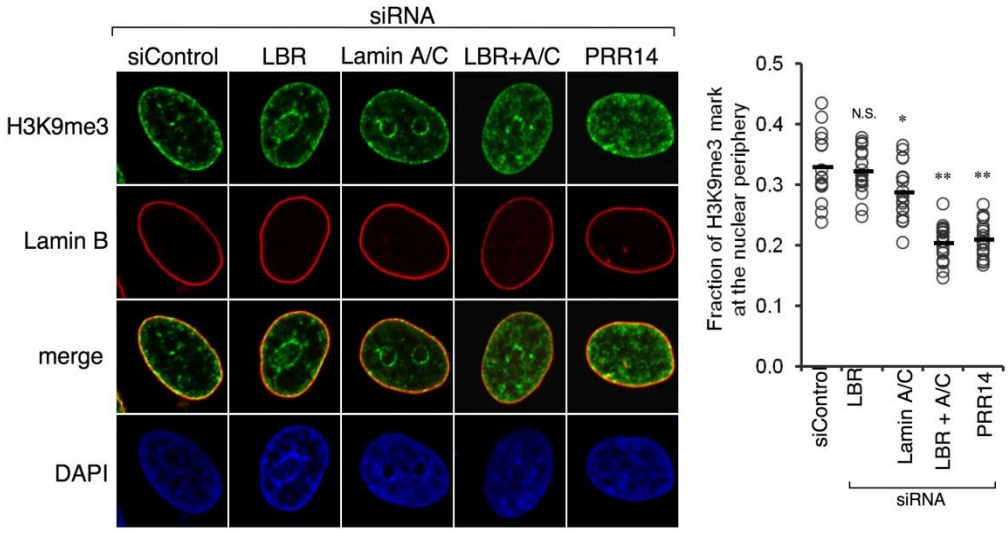

Figure 8. PRR14 provides an essential function in tethering H3K9me3-marked heterochromatin to the nuclear lamina. SiRNA knockdown of PRR14 causes disruption of peripheral heterochromatin. Knockdown of another heterochromatin tethering protein, LBR, or Lamin A/C has no significant effect. Quantification of heterochromatin redistribution is shown at the right.

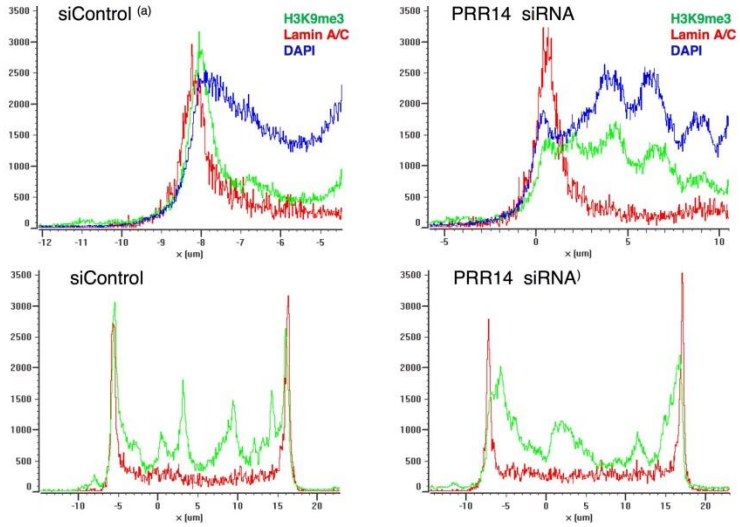

Figure 9. Line scans of images showing release of heterochromatin (blue/green) from the nuclear lamina (red) after PRR14 siRNA knockdown. Top panels: Scan of nuclear rim. Bottom panels: Scan of the entire nucleus.

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

Note: Studies that fall dramatically short on recruitment are encouraged to provide the details of their recruitment efforts in Item 17, Progress in Achieving Research Goals, Objectives and Aims. For example, the number of eligible subjects approached, the number that refused to participate and the reasons for refusal. Without this information it is difficult to discern whether eligibility criteria were too restrictive or the study simply did not appeal to subjects.

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 or paper submitted for publication, listed in the table, in a PDF version 5.0.5 (or greater) format, 1,200 dpi. Filenames for each publication should include the number of the research project, the last name of the PI, and an abbreviated title of the publication. For example, if you submit two publications for Smith (PI for Project 01), one publication for Zhang (PI for Project 03), and one publication for Bates (PI for Project 04),

the filenames would be:

Project 01 – Smith – Three cases of isolated
Project 01 – Smith – Investigation of NEB1 deletions
Project 03 – Zhang – Molecular profiling of aromatase
Project 04 – Bates – Neonatal intensive care

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. The human protein PRR14 tethers heterochromatin to the nuclear lamina during interphase and mitotic exit.	Poleshko, A., Mansfield, K.M., Burlingame, C.C., Andrake, M.D., Shah, N.R. Katz, R.A.	*Cell Reports* *Cell Rep*. 5:292–301, 2013.	May 2013	☐Submitted ☐Accepted ☒Published
2. Specifying peripheral heterochromatin during nuclear lamina reassembly.	Poleshko, A. and Katz, R.A.	*Nucleus* *Nucleus* 5:32–39, 2014.	Dec 2013	☐Submitted ☐Accepted ☒Published

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

Yes___X____ No_____

If yes, please describe your plans:

Studies are in progress to address additional mechanistic aspects of PRR14 function. We expect that publishable results will be obtained in the near future.

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.

A conserved organizational feature of eukaryotic nuclei is the peripheral heterochromatin compartment, which provides a protected area for epigenetically silent genes and gene-poor DNA. In human cells this compartment is associated with the nuclear lamina, the protein meshwork at the inner edge of the nucleus. Heterochromatin-nuclear lamina interactions promote epigenetic gene silencing, and thereby can control many aspect of cell growth. Important biological roles for the nuclear lamina as a docking site for peripheral heterochromatin continue to emerge within many normal and disease processes, including development, cancer, aging, and cell senescence. We discovered that a previously unstudied human protein, PRR14, participates in the tethering of heterochromatin to the inner nuclear periphery. This is a major finding in that it provides insight into a critical, but poorly understood aspect of gene and chromatin organization.

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.

Richard A. Katz, Ph.D. (role: PI)
My experience and qualifications in the area of epigenetic research made me well-suited as PI for this project. I was drawn to the area of epigenetics through my long-term interest in retroviruses. As a retrovirologist, I have years of published experience in cell biology, biochemistry, and protein-DNA interactions. More recently, I demonstrated that epigenetically silent retroviral transgenes can serve as powerful probes to understand human epigenetic factor networks. I developed an siRNA-based functional screen to identify cell-wide factor networks that contribute to epigenetic gene silencing in human cells. The work relevant to the current application has been supported by consecutive NIH grants, first an exploratory R21 grant to establish the epigenetic screen methodology, followed by a three-year single-PI Epigenomics Roadmap R01 grant to implement a genome-wide siRNA screen. The output of this screen has served as a hypothesis generating tool. The experiments described in this application are based largely on a protein factor discovered in this screen, which functions in heterochromatin organization and dynamics. Overall, I have extensive experience in epigenetic research, all aspects of research supervision, laboratory management, and mentoring. Furthermore, our recently published work as well as additional preliminary results described in this application, have demonstrated that my laboratory can effectively implement new cell biological techniques. My laboratory is also carrying out other free-standing epigenetic studies, focusing on the role of epigenetic factors in human melanoma, and the effects of dietary compounds epigenetic processes. I have applied for NIH and private support for both of these projects. Based on my interests and productivity in the area of epigenetics, I was invited to be a founding member of the FCCC Epigenetics and Progenitor Cells Keystone Program, and I am currently a member of the FCCC Cancer Epigenetics Program. In summary, I am highly qualified investigator and well positioned to continue to make significant contributions to understanding epigenetic control mechanisms in human cells.

B. POSITIONS

Postdoctoral Fellow, Department of Cell Biology, Roche Institute of, Molecular Biology, Nutley, NJ	1981-1983
Research Associate, Department of Molecular Oncology and Developmental Biology, Hoffmann-La Roche Inc., Nutley, NJ	1983-1985
Research Associate, Department of Molecular Oncology, Biology, Roche Institute of Molecular, Nutley, NJ	1985-1986
Research Fellow, Department of Molecular Oncology, Roche Institute of Molecular Biology, Nutley, NJ	1986-1987
Senior Research Associate, Laboratory Chief, Institute for Cancer Research, Fox Chase Cancer Center, Philadelphia, PA	1987-1997
Staff Scientist, Laboratory Chief, Institute for Cancer Research, Fox Chase Cancer Center, Philadelphia, PA	1997-2009
Research Professor, Institute for Cancer Research, Fox Chase Cancer Center, Philadelphia, PA	2009-present

RECOGNITION AND SERVICE – KATZ, RICHARD ALAN, Ph.D.

Summa Cum Laude, Syracuse University, Syracuse, NY	1975
Editorial Board, Journal of Virology	1987-1996
Editorial Board, Virology	1992-present
Ad hoc Reviewer, Aids and Related Research Study Section	1996
Session Co-Chairperson, Cold Spring Harbor Retrovirus Meeting	1992, 1996, 1999
Ad hoc Reviewer, U.S.-Israel Binational Science Foundation	2004
Ad hoc Reviewer, The Israel Science Foundation	2005
Ad hoc Reviewer, Italian Telethon Foundation	2006
Ad hoc Reviewer, The Wellcome Trust	2009
Member, NIH Special Emphasis Panel ZRG1 AARR-D (04) M	2009
Member, NIH Special Emphasis Panel ZRG1 EMNR-E (02) M	2011
Member, NIH Special Emphasis Panel ZRG1 AARR-C(04) M	2012
Editorial Board, Journal of Virology	2014-2016

Ad hoc Reviewer (solicited by journal): ACS Chemical Biology, American Journal of Pathology, Analytical Biochemistry, Biochemistry, Biochemical Journal, Epigenetics, Gene, Journal Biological Chemistry, Journal of Clinical Investigation, Journal of General Virology, Journal of Virology, Molecular Pharmacology, Nature Reviews Microbiology, Nucleic Acids Research, PLoS Biology, PLoS ONE, PLoS Computational Biology, PLoS Pathogens, Proceedings of the National Academy of Science U.S.A., Retrovirology, Theriogeneology, Trends in Genetics

PROGRAM AND WORKING GROUP AFFILIATIONS

Member, Viral Pathogenesis Working Group, Fox Chase Cancer Center	2003-2008
Participant, Genome Stability Working Group, Fox Chase Cancer Center	2006-present
Primary Member, Epigenetics and Progenitor Cells Keystone Program, Fox Chase Cancer Center	2007-present
Primary Member, Cancer Biology Program, Fox Chase Cancer Center	2009-2012
Member, Cancer Epigenetics Program, FCCC-TUSM	2012-present

SOCIETIES

American Association for Cancer Research
American Society for Microbiology
American Society for Virology