

# 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:** Temple University of the Commonwealth System of Higher Education
2. **Reporting Period (start and end date of grant award period):** 01/01/2009 – 12/31/2012
3. **Grant Contact Person (First Name, M.I., Last Name, Degrees):** Germaine A Calicat
4. **Grant Contact Person’s Telephone Number:** 215.204.7655
5. **Grant SAP Number:** 4100047651
6. **Project Number and Title of Research Project:** 11 - RAD51 Causes Genomic Instability in Chronic Myeloid Leukemia
7. **Start and End Date of Research Project:** 01/01/2009 - 12/31/2010
8. **Name of Principal Investigator for the Research Project:** Tomasz Skorski, MD, PhD, DSc
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:

\$64,453

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
Dasgupta, Y.	Graduate Assistant	100% Yr 1	\$16,092
Gillespie, E.	Graduate Assistant	1% Yr 2	\$557
Nieborowska-Skorska	Research Scientist	1% Yr 2	\$3,624
Ray, R.	Technician	50% Yr 1, 50% Yr.3	\$27,657
Kopinski, P.	Technician	1% Yr 2	\$1,582
Penserga, E.	Student Worker	1% Yr 2	\$1,045

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
Skorski, T.	Professor	<1%

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  \_\_\_\_\_

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  \_\_\_\_\_

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:
RAD51 causes genomic instability in CML	xNIH <input type="checkbox"/> Other federal (specify:_____) <input type="checkbox"/> Nonfederal source (specify:_)	03/2009	\$375,000	\$0
DNA recombination in CML progression	xNIH <input type="checkbox"/> Other federal (specify:_____) <input type="checkbox"/> Nonfederal source (specify:_)	10/2009	\$375,000	\$0

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:

Submit a new R01 application to NIH.

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

We will continue to develop the small peptide aptamer technology to target tumor cells.

**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	2			
Female			2	
Unknown				
<b>Total</b>	<b>2</b>		<b>2</b>	

	Undergraduate	Masters	Pre-doc	Post-doc
Hispanic				
Non-Hispanic	2		2	
Unknown				
<b>Total</b>				

	Undergraduate	Masters	Pre-doc	Post-doc
White	1		1	
Black				
Asian	1		1	
Other				
Unknown				
<b>Total</b>				

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

Yes \_\_\_\_\_ No  \_\_\_\_\_

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 \_\_\_\_\_ No  \_\_\_\_\_

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

**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  \_\_\_\_\_

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 ( $\alpha$ ) and beta ( $\beta$ ) should not print as boxes ( $\square$ ) and include the appropriate citation(s). DO NOT DELETE THESE INSTRUCTIONS.**

Specific Aim #1

- 1) Using SKY analysis we showed that downregulation of the over-expressed RAD51 in BCR/ABL-positive leukemia cells reduced the accumulation of chromosomal translocations and truncations by 3-fold/metaphase after irradiation. Overall, 9 different chromosomal aberrations were detected in cells incubated with scrambled RNA (elevated RAD51); conversely only 2 abnormalities were detected in these incubated with siRNA targeting RAD51.
- 2) As determined by co-immunoprecipitation assay BCR/ABL-RAD51 interaction was not blocked by peptide aptamers containing proline-rich fragments of RAD51
- 3) The aptamer containing phospho-Y315 of RAD51 reduced chromosomal instability in BCR/ABL positive leukemia (measured by SKY analysis). These studies will be continued.

Specific Aim #2

DNA polymerase beta was not downregulated by the expression plasmid carrying the shRNA.

**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  
 No

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

Yes  
 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, 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. None				<input type="checkbox"/> Submitted <input type="checkbox"/> Accepted <input type="checkbox"/> Published

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

Yes  No

If yes, please describe your plans:

We will continue to examine the role of RAD51 phospho-Y315 in accumulation of chromosomal aberrations in leukemias induced by BCR/ABL kinase. These studies may lead to future publication.

**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

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.*

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## BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

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NAME Skorski, Tomasz	POSITION TITLE Professor		
eRA COMMONS USER NAME tskorski			
INSTITUTION AND LOCATION	DEGREE (if applicable)	YEAR(s)	FIELD OF STUDY
Medical Academy, Warsaw, Poland	M.D.	1982	General Practice
Medical Center of Postgraduate Education, Warsaw, Poland	Ph.D.	1985	Immunology/ Oncology
Medical Center of Postgraduate Education, Warsaw, Poland	D.Sc.	1990	Oncology/ Hematology

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### A. PERSONAL STATEMENT

We and others found that cancer cells accumulate potentially lethal DNA double-strand breaks (DSBs), but homologous recombination repair (HRR) and non-homologous end-joining (NHEJ) protect their survival. Normal cells use BRAC1/2-dependent HRR and DNA-PK –mediated NHEJ to prevent DSB-triggered apoptosis. However, cancer cells may employ RAD52-mediated HRR and PARP1-mediated NHEJ. These changes may be driven by genetic and epigenetic aberrations. We explore these differences to target tumor-specific DNA repair mechanisms to achieve “*synthetic lethality*” in cancer cells, with negligible effect on normal cells.

### B. POSITIONS AND HONORS

1982-1985 Post-doctoral fellow, Department of Cytophysiology, Medical Center of Postgraduate Education, Warsaw, Poland

1985-1990 Staff Scientist, Department of Cytophysiology, Medical Center of Postgraduate Education, Warsaw, Poland

1990-1991 Postdoctoral Fellow, Temple University School of Medicine, Department of Pathology and Fels Institute for Molecular Biology and Cancer Research, Philadelphia, PA

1991-1992 Postdoctoral Fellow, Thomas Jefferson University Hospital, Jefferson Cancer Institute, Philadelphia, PA

1992-1994 Research Instructor, Department of Microbiology/Immunology, Jefferson Cancer Institute, Thomas Jefferson University, Philadelphia, PA

1994-08/99 Research Assistant Professor, Department of Microbiology/Immunology, Kimmel Cancer Institute, Thomas Jefferson University, Philadelphia, PA

09/99-10/05 Associate Professor, Center for Biotechnology, College of Sciences and Technology, Temple University, Philadelphia, PA

11/05-06/06 Associate Professor, Department of Microbiology and Immunology, School of Medicine, Temple University, Philadelphia, PA

07/2006-pres. Professor, Department of Microbiology and Immunology, School of Medicine, Temple University, Philadelphia, PA

02/2012-pres. Associate Professor, Fels Institute for Cancer Research and Molecular Biology, Temple University School of Medicine, Philadelphia, PA

### AWARDS and FELLOWSHIPS

1992 Cancer Research Foundation of America - Fellowship

1995, 1997	Elsa U. Pardee Cancer Research Awards
1997-2000	New Investigator Research Award (R29), National Cancer Institute
2000-2005	Scholar of the Leukemia and Lymphoma Society
2003	American Cancer Society Research Scholar
2005	Stohlman Scholar of the Leukemia and Lymphoma Society
2006	Temple University School of Medicine Dean's Award for outstanding faculty achievements
2008	Medallion of Amici of Universitas Lodziensis, Poland

### PROFESSIONAL ACTIVITIES

2003-	Ad-hoc reviewer for NIH
2005, 2008	Department of Defense, Research Program review
2005-2011	Leukemia and Lymphoma Society, member of the review panel
2007, 2011	Abstract reviewer for ASH
2008	Co-Chairperson, Program Committee Planning for 2009 AARC Meeting
2011-	Member of TCB Study Section at NIH
2012	Coordinating ASH Abstract Reviewer of the scientific category 601-- Chromosomal Rearrangements and DNA Repair.

### C. PEER-REVIEWED PUBLICATIONS (selected from 141):

1. Rink, L., Slupianek, A., Stoklosa, T., Nieborowska-Skorska, M., Urbanska, K., Seferynska, I., Reiss, K., Skorski, T. [Enhanced phosphorylation of Nbs1, a member of DNA repair/checkpoint complex Mre11-RAD50-Nbs1, can be targeted to increase the efficacy of imatinib mesylate against BCR/ABL-positive leukemia cells.](#) **Blood**, 110:651-660, 2007.
2. Koptyra, M., Cramer, K., Slupianek, A., Richardson, C., Skorski, T. [BCR/ABL promotes accumulation of chromosomal aberrations induced by oxidative and genotoxic stress.](#) **Leukemia**, 22: 1969-1972, 2008.
3. Cramer, K., Nieborowska-Skorska, M., Koptyra, M., Slupianek, A., Penserga, ET., Eaves, CJ., Aulitzky, W, Skorski, T. [BCR/ABL and other kinases from chronic myeloproliferative disorders stimulate single-strand annealing, an unfaithful DNA double-strand break repair.](#) **Cancer Res.**, 68: 6884-6888, 2008.
4. Perrotti D, Jamieson C, Goldman J, Skorski T. [Chronic myeloid leukemia: mechanisms of blastic transformation.](#) **J. Clin. Invest.**, 120:2254-64, 2010.
5. Slupianek A, Poplawski T, Jozwiakowski SK, Cramer K, Pytel D, Stoczynska E, Nowicki MO, Blasiak J, Skorski T. [BCR/ABL stimulates WRN to promote survival and genomic instability.](#) **Cancer Res.**, 71:842-51. 2011.
6. Slupianek A, Dasgupta Y, Ren SY, Gurdek E, Donlin M, Nieborowska-Skorska M, Fleury F, Skorski T. [Targeting RAD51 phosphotyrosine-315 to prevent unfaithful recombination repair in BCR-ABL1 leukemia.](#) **Blood**, 118:1062-8, 2011.
7. Skorski, T. [BCR-ABL1 kinase: hunting an elusive target with new weapons.](#) **Chem Biol.**, 18:1352-3, 2011.
8. Nieborowska-Skorska M, Kopinski PK, Ray R, Hoser G, Ngaba D, Flis S, Cramer K, Reddy MR, Koptyra M, Penserga T, Glodkowska-Mrowka E, Bolton E, Holyoake TL, Eaves CJ, Cerny-Reiterer S, Valent P, Hochhaus A, Hughes TP, van der Kuip H, Sattler M, Wiktor-Jedrzejczak W, Richardson C, Dorrance A, Stoklosa T, Williams DA, Skorski T. [Rac2-mitochondrial respiratory chain complex III-generated ROS cause genomic instability in chronic myeloid leukemia stem cells and primitive progenitors.](#) **Blood**, 119: 4253-63, 2012.
9. Flis K, Irvine D, Copland M, Bhatia R, Skorski T. [Chronic myeloid leukemia stem cells display alterations in expression of genes involved in oxidative phosphorylation.](#) **Leuk, Lymphoma**, 53:2474-8, 2012.
10. Slupianek A, Falinski R, Znojek P, Stoklosa T, Flis S, Doneddu V, Pytel D, Synowiec E, Blasiak J, Bellacosa A, Skorski T. [BCR-ABL1 kinase inhibits uracil DNA glycosylase UNG2 to enhance oxidative DNA damage and stimulate genomic instability.](#) **Leukemia**, 27:629-34, 2013.