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):** 1/1/2010-12/31/2013

3. **Grant Contact Person (First Name, M.I., Last Name, Degrees):** Germaine A Calicat, MA

4. **Grant Contact Person's Telephone Number:** 215.204.7655

5. **Grant SAP Number:** 4100050909

6. **Project Number and Title of Research Project:** Project 20 Egr-1 Tumor Suppressor of Chronic Myeloid Leukemia

7. **Start and End Date of Research Project**: 9/20/2011-9/19/2012

8. **Name of Principal Investigator for the Research Project:** Barbara Hoffman, PhD

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:

   $ 45,600.06

   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
Maifrede, Silvia	Graduate Student	100	$45,601 (includes fringe and indirect)

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
Hoffman, Barbara	Professor, Principal Investigator	30
Liebermann, Dan A.	Professor, Collaborator	10

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____X_____ No_____

If yes, please indicate the source and amount of other funds:
NIH, RO1, in No Cost Extension
NIH, RO1, CA122376-01A1; Salary support for B. Hoffman, 10%, and D. Liebermann, 30%
Bridge Funding, start 7/1/2012; $75,000
Bridge Funding (shared between Hoffman and Liebermann), 2.2011-2/2012- $30,000
MD Anderson SPORE funds: 6/2012-6/2013-, $30,00

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 to be awarded:
Tumor Suppressor EGR1 and Leukemia	xNIH ☐ Other federal (specify:_____ _____) ☐ Nonfederal source (specify: _____)	Feb, 2013	$2,300,000	$not funded
Tumor Suppressor Egr-1 in Leukemia	☐NIH ☐ Other federal (specify:_____ _____) x☐ Nonfederal source (specify: MD Anderson SPORE	June 2012	$63,000	$63,000

	Developmental Research Project_____)			
	☐NIH ☐ Other federal (specify:_____ _____) ☐ Nonfederal source (specify: _____)		$	$

The project was in its early stages prior to start date. Data obtained on tumor suppressor role of Egr1 in chronic myeloid leukemia provided me with data to submit proposals.

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:
I plan to submit a revision of the NIH RO1 with data obtained on human CML, as well as how loss of Egr1 altered cancer stem cells. This data was obtained using SPORE funds, and SPORE funds were awarded due to CURE formula funding.

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

Completion of mechanistic studies; analysis of gain of function of Egr1 in CML; expanding studies on tumor suppressor role of Egr1 in AML, analysis of regulation of Egr1 in human leukemia.

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	
Unknown				
Total			**1**	

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

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

Studying the tumor suppressor role of Egr1 in leukemia is unique and has not been done at Temple. My graduate student was invited to give an oral presentation of the research at the ASH annual conference in Dec, 2012 and I was invited to give an oral presentation and the prestigious preAHS Myeloid Workshop in Dec, 2013.

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:
It is hypothesized that Egr-1 acts as a tumor suppressor against BCR/ABL driven leukemia. Accordingly, **we will test our predictions that loss of Egr-1 will accelerate the initiation and progression of CML**. Applying novel mouse models and human tissue samples, in conjunction with state of the art molecular and cell biological approaches the following aims will be addressed: **Aim 1** will determine the effect of loss of Egr-1 on initiation and progression of leukemia using diseased mice, and what transpires at early times after BCR/ABL is expressed in BM null for Egr-1 compared to WT BM. In vitro analysis will use BCR/ABL expressing BM that has not been transplanted into mice. In **Aim 2**, studies will determine the molecular mechanism of how loss of Egr-1 accelerates BCR/ABL mediated leukemia. Signaling pathways and Egr-1 target genes in cells from both leukemic mice and maintained in culture will be determined. **Aim 3** will determine how loss of Egr-1 affects the response to different drug treatments**.** **Aim 4** will extend the study from mice to humans. Human CML samples will be screened for Egr-1 expression and down-stream effectors.

Summary of Research Completed

Transduction/transplantation (bone marrow transplantation [BMT]) protocol: The Phoenix virus packaging cell line was transiently transfected with appropriate vectors (MigR1-BCR-ABL or MigR1 [empty vector]) and infectious supernatant collected 48 hours later; vectors contain an internal ribosome entry site (IRES)-GFP cassette. Donor bone marrow (BM) cells were derived from 5-fluorouracil {(5-FU, 200mg/kg) for 4days} treated, age-matched (8 weeks) wild type (WT) and Egr-1 null mice (C57BL/6; obtained from Dr. Michelle LeBeau [University of Chicago)]). Following expansion in medium (expansion medium [EM]) with 10% FBS, IL-6 (10ng/ml), IL-3 (20ng/ml) and SCF (20ng/ml) for 24 hours, bone marrow (BM) from both WT and Egr-1 null mice were either mock infected or infected with either MigR1 or MigR1-BCR/ABL by two rounds of spinoculation with retroviral supernatants in the presence of 5 ug/mL polybrene. Recipient WT mice were sub-lethally irradiated (850 rad) and the following day mice were injected with BM cells (1.5-2.5x10^6 total; same percentage of GFP positive cells for each transplantation) by retro-orbital injection. Mice each were transplanted with MigR1-BCR/ABL, WT BM or MigR1-BCR/ABL, Egr-1 null BM. In addition, for control groups, mice were transplanted with empty-vector infected BM (WT and Egr-1 null) or mock-infected BM (WT and Egr-1 null), and a group of mice were irradiated without transplantation.

Assessment of mice following BMT. Mice were monitored 3 times/week by palpitation & observation. Mice were monitored for signs of leukemia, including cachexia, decreased movement, including hind limb paralysis, and poor grooming. Terminally ill mice were euthanized & analyzed. Liver, spleen, BM and peripheral blood were analyzed.

1. Three independent experiments (Fig. 1, Table 1) clearly show that loss of Egr-1 accelerated the onset and progression of chronic myeloid leukemia (CML). For the survival curve shown in Fig. 1, the median time of death for Egr-1 KO (knock-out; null) mice was 28 days after transplantation, and for WT mice it was on day 43. Furthermore, all Egr-1 KO-transplanted mice were terminally ill by 43 days, whereas for WT mice this occurred by 56 days post BMT. A summary of two additional independent experiments (Table 1) shows similar results.

2. In addition, the livers from moribund Egr-1 null BM transplanted mice were significantly larger than from mice transplanted with Egr-1 WT BM, and there was no detectable difference in the size of the spleen (Table 2).

3. BM removed from moribund mice was maintained in culture, and assessed for cell number, using the MMT {3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, a yellow tetrazole)} assay, and apoptosis by annexinV & 7AAD staining follow by flow cytometry.

At this stage more than 90% of the cells were GFP positive. Data shows that Egr-1 null BM expressing BCR/ABL proliferates more rapidly than its wild type counterpart (Fig. 2A). In addition, there is reduced apoptosis in Egr-1 null cells compared to WT cells (Fig. 2B). These data show that loss of Egr-1 results in increased number of cells and reduced cell death. The increased cell numbers can be accounted for at least partially by reduced apoptosis; however, DNA synthesis must be determined as well.

3. Cell extracts from cultured BM cells obtained from leukemic mice were used to assess the expression of p-AKT and total AKT. Activation of the P13k/Akt/mTOR pathway is crucial for maintenance of CML. Egr-1 impacts on this pathway by regulating the phosphatase Pten, which in turn negatively regulates signaling through the phosphatidylinositol-3-OH kinase (PI-3kinase; PI3k) pathway. Extracts from GFP+ BM confirm increased p-AKT in Egr-1 null cells expressing BCR/ABL compared to WT counterparts (Fig. 2C).

Comparison of Egr-1 null/BCR/ABL BM with wild type counterparts at 18 days post BMT. In order to compare the progression of leukemia in the presence or absence of Egr-1, BM was taken from transplanted mice at 18 days post BMT, rather than when mice are moribund. GFP positive BM was analyzed for markers associated with early progenitors/stem cell populations. Specifically, cells that are lineage negative were further sorted for those that were Sca-1+, c-Kit+ (LSK). Assessment of BM revealed that there are more early progenitors in mice transplanted with Egr-1KO-p210 BM compared to WT counterparts (Fig. 3). Furthermore, enlargement of spleen was observed in Egr-1 null transplanted mice by day 18 relative to WT mice at day 18. These data show that by day 18, mice with Egr-1 null BCR/ABL BM are exhibiting more advanced stages of disease compared to WT counterparts.

Is the leukemia caused by Egr-1KO/BCR/ABL bone marrow transplantable to healthy mice? It has been shown that BM from the CML mouse model can transplant CML to healthy mice, but BM from these secondary transplants cannot transfer the disease. To assess if Egr-1 null BM can transplant the leukemia, BM from primary transplants was removed 15 days post BMT and transplanted to irradiated mice, and was assessed for survival. The data show that the leukemia

from Egr-1 null/BCR/ABL primary transplants can indeed be transplanted to healthy mice. In addition, the secondary transplanted mice using Egr-1 null BM become moribund much more rapidly than WT counterparts (Fig. 4), thereby preventing continuing the serial transplantation to determine how many serial transplants would be possible for Egr-1 null leukemic BM.

Aim 1 was accomplished, and part of aim 2. Research addressing aims 3 and 4 was not undertaken. The four aims included in the original grant's research plan were part of our long-term plan, and it was not possible to determine exactly what could be accomplished within the one year funding period.

Abstracts accepted after peer review

Maifrede S, Sha X, Liebermann D and Hoffman B. Loss of EGR-1 accelerates BCR-ABL-driven leukemogenesis. Blood (ASH Annual Meeting Abstracts; Peer Reviewed) 118:1671, 2011.

Maifrede S, Liebermann D and Hoffman B. Stress response gene Egr-1 as tumor suppressor in BCR-ABL mediated leukemia. Blood (ASH Annual Meeting Abstracts; Peer Reviewed) 120:33, 2012. Selected for oral presentation.

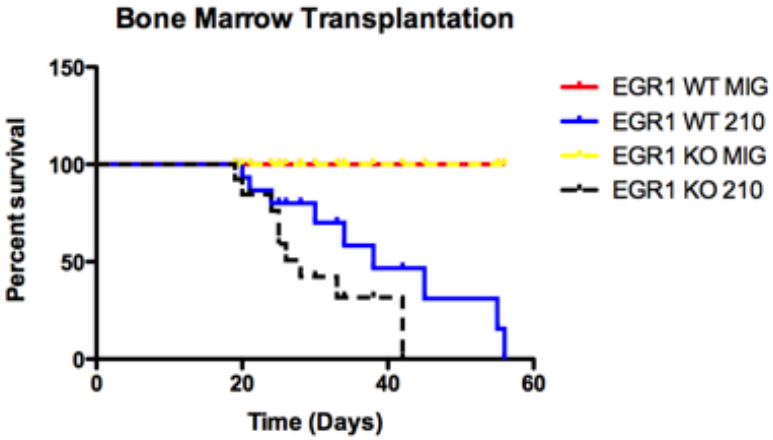

Figure 1. Bone marrow transplantation survival curve.

Exp. # 1

Genotype	N =	First death	Median	Last Death
Egr-1 KO Bcr/Abl	8	BMT day 15	25	33
Egr-1 WT Bcr/Abl	7	BMT day 35	45	55

Exp. # 2

Genotype	N =	First Death	Median	Last Death
Egr-1 KO Bcr/Abl	12	BMT day 15	22	35
Egr-1 WT Bcr/Abl	7	BMT day 25	35	45

Table 1. Summary from two independent experiments to obtain bone marrow survival.

Genotype	Total Body Weight (g)	Liver (g)	Spleen (g)	% TBW Liv.	% TBW Sp.
WT BCR-ABL	22.1	0.94	0.44	4.74	1.99
WT BCR-ABL	19.9	1.17	0.09	7.69	0.48
WT BCR-ABL	15.2	0.98	0.33	5.13	2.21
Average	19.0	1.03	0.29	5.86	1.56
STDEV	2.87	0.09	0.14	1.30	0.76
KO BCR-ABL	18.6	1.15	0.36	6.18	1.93
KO BCR-ABL	21.5	2.07	0.53	9.62	2.47
KO BCR-ABL	20.4	1.37	0.16	6.71	0.78
KO BCR-ABL	28.8	2.1	0.19	7.29	0.65
Average	22.32	1.67	0.31	7.45	1.46
STDEV	4.47	0.48	0.17	1.51	0.88
Empty vector	26.5	1.4	0.08	5.28	0.30
Not Transpl.	26.6	1.44	0.08	5.41	0.30

Table 2. Analysis of spleen and liver size of moribund mice.

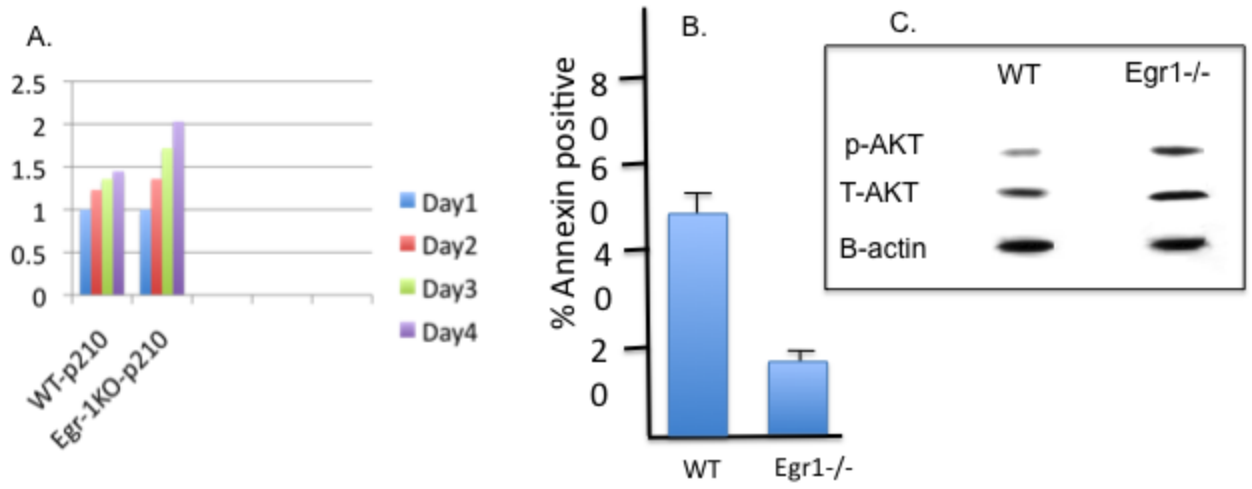

Figure 2. Analysis of bone marrow obtained from leukemic mice and maintained in culture. A. MMT assay. B. Apoptosis determined by annexin positive cells. C. Western blotting using extracts from GPF+ cells to assess p-AKT and total AKT levels.

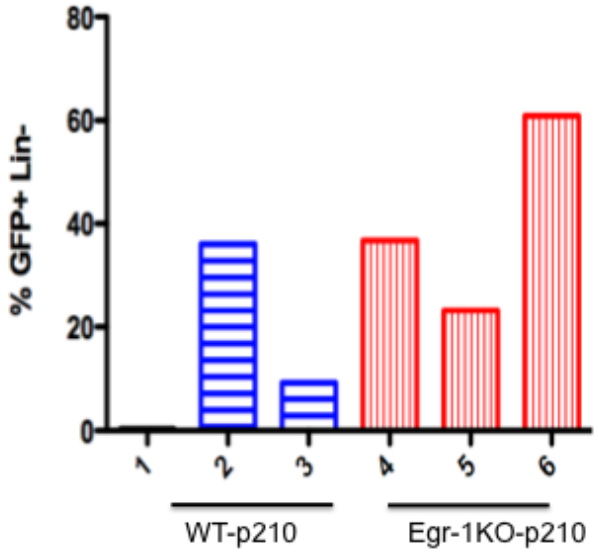

Figure 3. Determination of level of early progenitors from transplanted mice 18 days post BMT. Mice were euthanized 18 days post BMT and % GFP+ve cells that were Lineage (Lin) negative was determined.

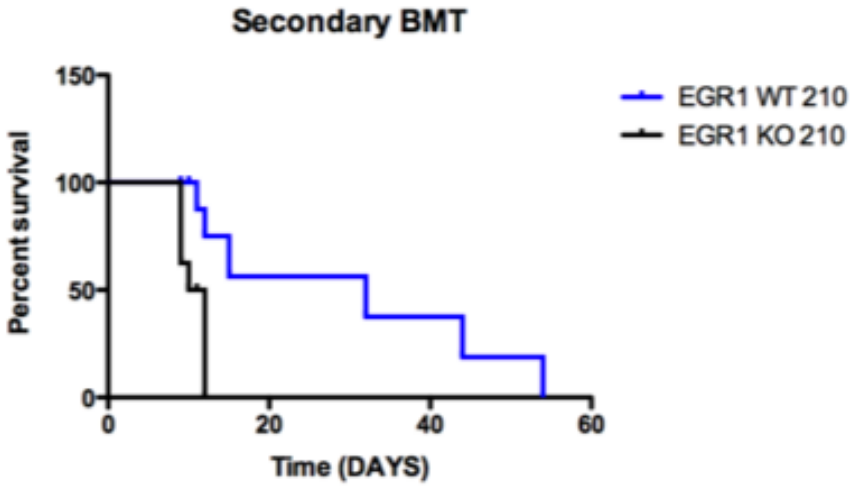

Figure 4. Survival curve of mice from secondary BMT.

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.				☐Submitted ☐Accepted ☐Published
2.				☐Submitted ☐Accepted ☐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:

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

Provide the following information for the Senior/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.**

NAME Hoffman, Barbara	POSITION TITLE Professor
eRA COMMONS USER NAME (credential, e.g., agency login)	

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
Brooklyn College, Bklyn, NY	BS	1968	Biology
University of Michigan, Ann Arbor, MI	MS, PhD	1970, 1973	Genetics
Weizmann Institute, Rehovoth, Israel	Postdoc	1974-76 1976-80	Virology Genetics
Stanford University, Stanford, CA	Postdoc	1980-85	Molecular Biology

A. Personal Statement

I have a longstanding interest in understanding how normal cells are converted to cancer cells, and for much of my scientific career I have focused this interest on hematopoiesis and leukemia as a paradigm for studying malignancy. I cloned myeloid differentiation primary response (MyD) genes, including novel genes MyD88 and MyD118 (Gadd45b), and also Gadd45g (CR6); one of the MyD genes was Egr-1. My laboratory has done extensive analysis of both positive and negative regulators of myeloid differentiation, to understand normal hematopoiesis as well as how blocks in differentiation and apoptosis participate in the initiation and progression of leukemia. We have shown how deregulated expression of negative regulators of differentiation blocks differentiation, and have extensively studied how deregulated c-myc prematurely activates an apoptotic response. Several exciting publications describe our studies on Egr-1 driving myeloid differentiation and overriding the block in differentiation due to deregulated E2F-1 or myc, which also resulted in blocking leukemia. The stress response gene family Gadd45 has also become a focal point over the last several years, understanding how it works at the molecular and cellular level, and what its role is in response to stress. Within the last 5 years my laboratory has studied the role of gadd45 in response to oncogenic stress, using breast cancer and leukemia mouse models. Within the last 3 years my laboratory has started to extensively utilize bone marrow transplantation (BMT) to further analyze the effect of stress response/tumor suppressor Egr-1 and the stress response Gadd45 family of genes. This has been done for transforming BCR/ABL, N-Ras and c-Myc. My goal is to decipher the role and the molecular/genetic mechanism of the tumor suppressor/stress response gene Egr-1 and the stress sensor gadd45 gene family in response to oncogenic stress. My long-term goal is to translate acquired knowledge to human disease. I have a publication record of over 135 manuscripts, have mentored over 30 postdoctoral trainees in my laboratory and was thesis advisor to 15 PhD students. In addition, I have also participated in mentoring over 50 PhD students either rotating in my laboratory or by participating in their thesis committees.

B. Positions and Honors

List in chronological order previous positions, concluding with the present position. List any honors. Include present membership on any Federal Government public advisory committee.

Positions and Employment

1974-1976 NIH Postdoc. Fellow, Dr. Ernest Winocour, Dept. of Virol., Weizmann Inst. of Sci., Rehovoth, Israel

1976-1980 Postdoc. Scholar, Dr. Leo Sachs, Dept. of Genetics, Weizmann Inst. of Science, Rehovoth, Israel

1978-1979 Israel Cancer Research Fund Fellow

1980-1985 Postdoc. Scholar, Dr. Stanley Cohen, Department of Genetics, Stanford, CA

1986-1993 Asst. Professor, Department of Biochemistry & Biophysics, School of Medicine, Univ. of PA

1993-2000 Assoc. Professor, Fels Institute and Dept. of Biochem., Temple Univ. School of Medicine, Phil., PA

2000-Present Professor, Fels Institute and Dept. of Biochem, Temple Univ. School of Medicine, Phil., PA

Other Experience and Professional Memberships

Sigma Xi; American Society for Microbiology; Philadelphia Cancer Research Association
American Association for Cancer Research; American Society of Hematology
Ad Hoc Reviewer, Hematology 2 Study Section, 1993; PO1 study section for NCI-NIH, 2008; III study section, 2010; Challenge grant reviewer;
Ad Hoc member, NIH Study Section, T30, T32 applications, July, 2011
Ad Hoc member, NIH Study Section, Cancer Prevention RO3, July, 2011
Ad Hoc, NIH Study Section, Basic Mechanisms of Cancer Therapeutics, Feb, 2012;
NIH reviewer, Special Emphasis panel predoctoral fellowships, basic, translational & clinical oncology, March, 2012
NIH reviewer, Special Emphasis panel, Oncology Fellowships, pre & post-doctoral, July, 2012
US-Israel Binational ScienceFoundation grant reviewer; Editorial Board, Oncogene

C. Selected Peer-reviewed Publications (from Total of 137)

Nguyen, H., Hoffman-Liebermann, B. & Liebermann, D.A. The zinc finger transcription factor EGR-1 is essential for and restricts differentiation along the macrophage lineage. Cell, 72:197-209, 1993

Shafarenko M, Liebermann DA, & Hoffman B. Egr-1 abrogates the block imparted by c-myc on terminal M1 myeloid differentiation. Blood 106: 871-878, 2005

Krishnaraju, K., Hoffman, B. and Liebermann, D.A. The zinc finger transcription factor Egr-1 activates macrophage differentiation in M1 Myeloblastic Leukemia Cells. Blood 92:1957-1966, 1998.

Krishnaraju K, Hoffman B, Liebermann DA. Early growth response gene 1 stimulates development of hematopoietic progenitor cells along the macrophage lineage at the expense of the granulocyte and erythroid lineages. Blood 97:1298-305, 2001

Gupta S, Gupta M, Hoffman B and Liebermann DA. Hematopoietic cells from gadd45a deficient and gadd45b deficient mice exhibit impaired stress responses to acute stimulation with cytokines, myeloablation, and inflammation. Oncogene, 25:5537-46, 2006. PMID: 16732331

Gupta M, Hoffman B and Liebermann DA. Gadd45a and gadd45b protect hematopoietic cells from ultraviolet radiation induced apoptosis via distinct signaling pathways including P38 activation and JNK inhibition. J Biol Chem. 281:17552-8, 2006. PMID: 16636063

Tront J, Hoffman B and Liebermann DA. Gadd45a Suppresses Ras-driven Mammary Tumorigenesis by Activation of JNK and p38 Stress Signaling Resulting in Apoptosis and Senescence. Cancer Research, 66:8448-54, 2006. PMID: 16951155

Liebermann DA and Hoffman B. Myeloid progenitors on demand. Nature Methods 3, 248-249, 2006. PMID: 16554827

Liebermann DA and Hoffman B. Gadd45 in the response of hematopoietic cells to genotoxic

stress. Blood Cells Mol Dis. 39:329-35, 2007. PMID: 17659913
Gibbs JD, Liebermann DA and Hoffman B. Terminal myeloid differentiation is uncoupled from cell cycle arrest. Cell Cycle 6:1205-9, 2007.
Hoffman B and Liebermann DA. Role of gadd45 in myeloid cells in response to hematopoietic stress. Blood Cells Mol Dis. 39:344-7, 2007. PMID 17686638
Gibbs JD, Liebermann DA and Hoffman B. Egr-1 abrogates the E2F-1 block in terminal myeloid differentiation and suppresses leukemia. Oncogene 27:98-106, 2008.
Gibbs JD, Liebermann DA and Hoffman B. Leukemia suppressor function of Egr-1 is dependent on transforming oncogene. Leukemia 22:1909-16, 2008. PMID: 17495532
Hoffman B, Liebermann DA. Apoptotic signaling by c-MYC. Oncogene 27:6462-72, 2008. PMID: 18955973
Hoffman B, Liebermann DA. Gadd45 modulation of intrinsic and extrinsic stress responses in myeloid cells. J Cell Physiol. 218:26-31, 2009. PMID: 18780287 [
Engel N, Tront JS, Erinle T, Nguyen N, Latham KE, Sapienza C, Hoffman . and Liebermann DA. Conserved DNA methylation in Gadd45a(-/-) mice. Epigenetics 4:98-99, 2009. PMID: 19229137
Xiong Y, Liebermann DA, Tront JS, Holtzman EJ, Huang Y, Hoffman B and Geifman-Holtzman-O. Gadd45a stress signaling regulates sFlt-1 expression in preeclampsia. J. Cell Physiol. 220:632-9, 2009. PMID: 19452502 PMID:
Cretu A, Sha X, Tront JS, Hoffman B. and Liebermann DA. Stress sensor gadd45 genes as therapeutic targets in cancer. Cancer Therapy 7:268-276, 2009. PMID: 19652693
Zumbrum S, Hoffman B, Liebermann DA. Distinct mechanisms are utilized to induce stress sensor gadd45b by different stress stimuli. J Cell Biochem. 108:1220-31, 2009. PMID: 19834918
Engel N, Tront JS, Erinle T, Nguyen N, Latham KE, Sapienza C, Hoffman . and Liebermann DA. Conserved DNA methylation in Gadd45a(-/-) mice. Epigenetics 4:98-99, 2009.
Tront JS, Yajue , Fornace A, Hoffman B, and Liebermann DA. Gadd45a Promotes or Suppresses Breast Cancer Dependent on the Oncogenic Stress. Cancer Research, 70:9671-81, 2010. PMID: 21098706.
Liebermann DA, Tront JS, Sha X, Mukherjee K, Mohamed-Hadley A & Hoffman B. Gadd45 Stress Sensors in Malignancy and Leukemia. Crit Rev Oncog. 2011. 16:129-40.
Tian J, Huang H, Hoffman B, Liebermann DA, Ledda-Columbano GM, Columbano A, Locker J. Gadd45B is an inducible coactivator of transcription that facilitate rapid liver growth in mice. J. Clin Invest. 121:4491-502, 2011. PMID:21965327.
Liebermann DA, Hoffman B. Prostate cancer: JunD, Gadd45a and Gadd45g as therapeutic targets. Cell Cycle, 10:3428, 2011. PMID: 22030693
Salerno DM, Tront JS, Hoffman B, Liebermann DA. Gadd45a and Gadd45b modulate innate immune functions of granulocyutes and macrophages by differential regulation of p38 and JNK signaling. J Cell Physiol. 227:3613-20, 2012. PMID: 22307729.
Xiong Y, Liebermann DA, Holtzman EJ, Hoffman B and Geifman-Holtzman-O. Preeclampsia Assoicated Stresses Activate Gadd45a Signaling and sFlt-1 in Placental Explants. J. Cell Physiol. 228:362-70, 2013.
Leach PT, Poplawski SG, Kenney JW, Hoffman B, Liebermann DA, Abel T, & Gould TJ. Gadd45b knockout mice exhibit selective deficits in hippocampus-dependent long-term Memory. Learning and Mem. 19:319-324, 2012.
Keil E, Hocker R, Schuster M, Essmann F, Ueffing N, Hoffman B, Liebermann DA, Pfeffer K, Schultze-Osthoff K, Schmitz I. Phosphorylation of Atg5 by the Gadd45b-MEKK4-p38 pathway inhibits autophagy. Cell Death Differ. 20:321-32, 2013.
Maifrede S, Sha X, Liebermann D and Hoffman B. Loss of EGR-1 accelerates BCR-ABL-driven leukemogenesis. Blood (ASH Annual Meeting Abstracts; Peer Reviewed) 118:1671, 2011.

Maifrede S, Liebermann D and Hoffman B. Stress response gene Egr-1 as tumor suppressor in BCR-ABL mediated leukemia. Blood (ASH Annual Meeting Abstracts; Peer Reviewed) 120:33, 2012. Selected for oral presentation.

Tront JS, Willis A, Huang Y, Hoffman B and Liebermann DA. Gadd45a levels in human breast cancer are hormone receptor dependent. J Transl Med. 11:131, 2013

Hoffman B, Liebermann DA. Gadd45 in modulation of solid tumors and leukemia. Adv Exp Med Biol. 793:21-33, 2013.

D. Research Support

CURRENT SUPPORT

Egr-1 Suppressor of Leukemia
Temple Bridge Funding, July 2012-June 2014
PI, B. Hoffman
Award: $75,000 official

Tumor Suppressor Egr-1 in Leukemia
Leukemia SPORE Developmental Research Award (administered by MD Anderson)
PI, B. Hoffman
Prime Award No. 5P50CA100632 10
National Cancer Institute
06/20/2012 - 04/30/2014
Award: $63,000 total costs

Gadd45 stress sensors in leukemia
Agency: NIH 1R01CA162403-01
PI: D. Liebermann; **Co-PI: B. Hoffman**,
Total Award: 1,038,000 direct costs, April, 2012-March 2017.

Recent Research Support:
Negative Regulators of Myelopoiesis
PI: B. Hoffman,
Agency: NIH 5 RO1 CA81168-08; Period: 4/1/99-06/30/11.
Gadd45 in the Response of Hematopoietic Cells to Stress
Co-PI: B. Hoffman, PI: D. Liebermann
Agency: NIH 1 RO1 HL084114-01A2; Period: 07/15/07-06/30/2011.

Gadd45 genes sensors of stress and tumor modulators 03/01/2007-02/29/2012
Co-PI: B. Hoffman, PI: D. Liebermann
Agency: NIH 1R01CA122376-01
Total Award: 1,150,000 direct costs