

# 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.

1. **Grantee Institution:** The Pennsylvania State University
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):** John Anthony, MPA
4. **Grant Contact Person’s Telephone Number:** 814 935 1081
5. **Grant SAP Number:** 4100050904
6. **Project Number and Title of Research Project:** 6. Bridging the Gap Between Label-Retention and Mammary Stem Cell Properties
7. **Start and End Date of Research Project:** 7/1/2010 - 6/30/2011
8. **Name of Principal Investigator for the Research Project:** Edward Gunther, MD
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:

\$ 46,530

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
None			

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
Gunther, Edward	Principal Investigator	2%
Gestl, Shelley	Research Technician	5%

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 \_\_\_\_\_ No X \_\_\_\_\_

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

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

A. Title of research project on grant application	B. Funding agency (check those that apply)	C. Month and Year Submitted	D. Amount of funds requested:	E. Amount of funds to be awarded:
None	<input type="checkbox"/> NIH <input type="checkbox"/> Other federal (specify: _____) <input type="checkbox"/> Nonfederal source (specify: _ )		\$	\$

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:

We are planning an R01 Grant Application for the last Cycle of 2014.

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

In future studies we will explore an alternative transgenic approach aimed at targeting H2B-GFP labeling to a larger population of mammary tumor cells. Specifically, we will test whether replacing the MMTV-rtTA transactivator with a ubiquitously expressed transactivator (*Gt(ROSA)26Sor<sup>tm1(rtTA\**M2*)Jae</sup>*) enables pervasive tumor cell labeling. This strategy ought to permit studies of proliferation-dependent H2B-GFP washout in Wnt tumor cells regardless of tumor cell configuration (i.e., in both hierarchically and biclonally configured tumors).

**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 \_\_\_\_\_ No   X  

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

	Undergraduate	Masters	Pre-doc	Post-doc
Male				
Female				
Unknown				
<b>Total</b>				

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

	Undergraduate	Masters	Pre-doc	Post-doc
White				
Black				
Asian				
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  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 project helped to expand the expertise and base of research studies related to breast cancer at the Penn State Hershey Cancer Institute.

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

A diverse set of observations suggest that stem cells within normal and malignant mammary epithelium may be capable of entering into and emerging from prolonged periods of quiescence. From a developmental biology perspective, the mammary gland resembles the hair follicle in that both evolved as ectodermally-derived skin appendages, and both can undergo a cyclical regenerative activity that is governed, at least in part, by the Wnt pathway. Provocatively, hair follicles are maintained by slow-cycling resident stem cells, though it is not yet clear whether mammary stem cells likewise cycle infrequently relative to other MECs. From a cancer biology perspective, it is clear that breast cancer patients frequently relapse after prolonged periods of clinically undetectable disease. Whether dormant breast cancer is comprised of quiescent cells versus cycling cells, whose proliferation is offset by cell death, remains unknown. When modeling dormant breast cancer by reversing Wnt1-initiated mammary tumorigenesis in transgenic mice, we found that minimal residual disease (MRD) lesions harbor both latent malignant potential and mammary gland reconstitution capacity. Moreover, our preliminary data demonstrate that MRD lesions harbor a slow-cycling MEC population. Based on these findings, we hypothesize that both normal and malignant mammary epithelium harbor a relatively quiescent MEC compartment with stem cell-like regenerative capacity. Here, we propose to demonstrate that these quiescent cells are enriched for expression of validated mammary stem cell markers by completing two Specific Aims. In Specific Aim 1, we will generate normal and neoplastic mammary tissue harboring H2B-GFP label-retaining cells (LRCs). In Specific Aim 2, we will determine whether H2B-GFP LRCs possess stem cell-associated biological features.

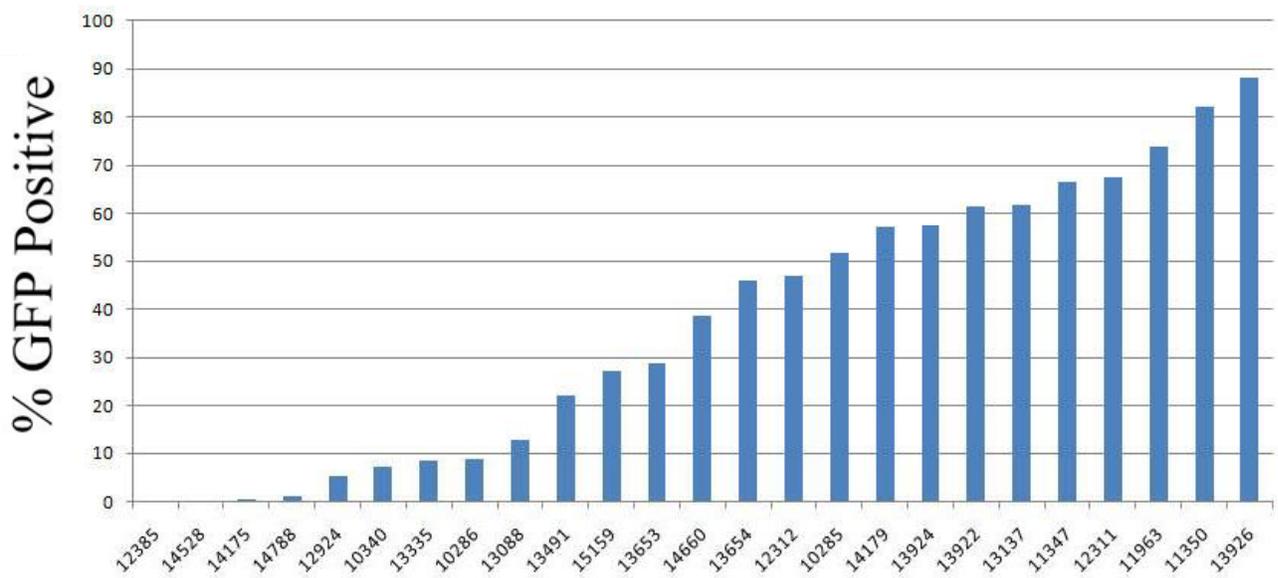
Testing a Strategy for labeling Wnt1-driven mammary tumors with H2B-GFP, a cell division-sensitive tracer. As a first step toward defining LRC populations within mammary tumors, we tested whether introducing the Tet-O-H2B-GFP transgene into the reversible Wnt-driven tumorigenesis model (MMTV-rtTA/Tet-O-Wnt1) would permit efficient labeling of tumor cells. A cohort of tri-transgenic female mice was generated and subjected to Dox treatment beginning at 6 weeks of age, then monitored for mammary tumor onset. When mammary tumors grew to 10 mm in diameter, biopsy samples were harvested, then minced, and subjected to enzymatic digestion to generate single cell suspensions. Flow cytometry then was performed to determine what fraction of tumor cells incorporated the fluorescent H2B-GFP label.

Although these tumors arose on genetically identical host mice, the extent of H2B-GFP labeling varied widely from tumor to tumor (Figure 1). Labeling of at least 20% of the tumor cell population was achieved in 16 of 25 tumors (64%), and labeling of at least 40% of the tumor cells was achieved in 12 of 25 tumors (48%). We sought to identify tumor characteristics that would predict a high labeling efficiency. Toward this end, we examined whether tumor latency

(the time elapsed between the initiation of Dox treatment to the detection of a tumor during twice-weekly monitoring) or the acquisition of a cooperating *HRas* mutation (observed in 16 of 25 tumors; 64%) correlated with labeling efficiency. Neither parameter was predictive, i.e., labeling efficiency was comparable in both early-onset versus late-onset tumors as well as *Hras*<sup>mutant</sup> versus *HRas*<sup>wild-type</sup> tumors.

Testing whether MRD lesions consistently harbor H2B-GFP LRCs. For a subset of the tumor-bearing MMTV-rtTA/Tet-O-H2B-GFP/Tet-O-Wnt1 mice in this cohort, we examined whether H2B-GFP labeled tumor cells persist within MRD lesions following Wnt withdrawal (Figure 2). Here, Dox-dependent mammary tumors were subjected to biopsy and biopsy specimens were processed and analyzed as described above to determine the extent of H2B-GFP labeling during ongoing Dox treatment. Then, tumor-bearing hosts were subjected to Dox withdrawal, which simultaneously initiates both tumor regression and proliferation-dependent H2B-GFP washout. MRD lesions were harvested at necropsy 6 to 8 weeks later, processed to generate single-cell suspensions, then analyzed by flow cytometry to determine the extent of persistent H2B-GFP labeling. The fraction of H2B-GFP LRCs within MRD lesions was highly variable. When compared against the extent of H2B-GFP labeling observed in antecedent tumors, most MRD lesions showed considerable washout with 9 of 13 (69%) MRD lesions showing at least a two-fold decrease in the fraction of labeled tumor cells. Interestingly, tumors that showed inefficient H2B-GFP labeling during Dox treatment tended to show less efficient washout. For example, the three tumor specimens that showed the lowest H2B-GFP labeling at biopsy all yielded MRD lesions that showed less than a two-fold decrease in labeled cells.

Unexpected levels of H2B-GFP labeling prompt consideration of alternative cellular configurations for Wnt-driven mammary tumors. The variable labeling efficiency and label retention identified in this work was unexpected and prompted us to reconsider the cellular configuration of Wnt-initiated mammary tumors. Wnt tumors have long been purported to arise from the transformation of bipotent mammary progenitor cells and to conform to a hierarchical configuration. Based in part on our H2B-GFP labeling studies, we proposed an alternative model in which some Wnt tumors might instead harbor lineage-committed subclones. We turned to immunophenotyping to resolve these putative subclones, and we were able to demonstrate that a subset of Wnt tumors indeed harbors genetically distinct basal and luminal subclones, effectively ruling out a hierarchical configuration for these tumors. Instead, we were able to show that this subset of Wnt tumors is biclonally configured. Furthermore, in follow up studies we discovered that biclonally configured Wnt tumors require cooperation between the component basal and luminal subclones for tumor maintenance and growth. These novel Wnt tumor findings provide the first demonstration of interclonal cooperation in a mammalian cancer.



**Figure 1. Flow cytometry reveals variable H2B-GFP labeling of mammary tumor cells.** Biopsy samples from 25 independent MMTV-rtTA/Tet-O-H2b-GFP/Tet-O-Wnt1 mammary tumors treated with Dox were prepared as single cell suspensions and analyzed for GFP+ tumor cell content by flow cytometry. The chart depicts the fraction of tumor cells exhibiting GFP positivity with each bar representing the flow cytometric measurement performed on a single independent mammary tumor. When frozen sections prepared from a group of representative tumors were examined by wide-field fluorescence microscopy, we found that the degree of GFP positivity measured by flow correlated well with the degree of GFP positivity visualized in situ (data not shown).

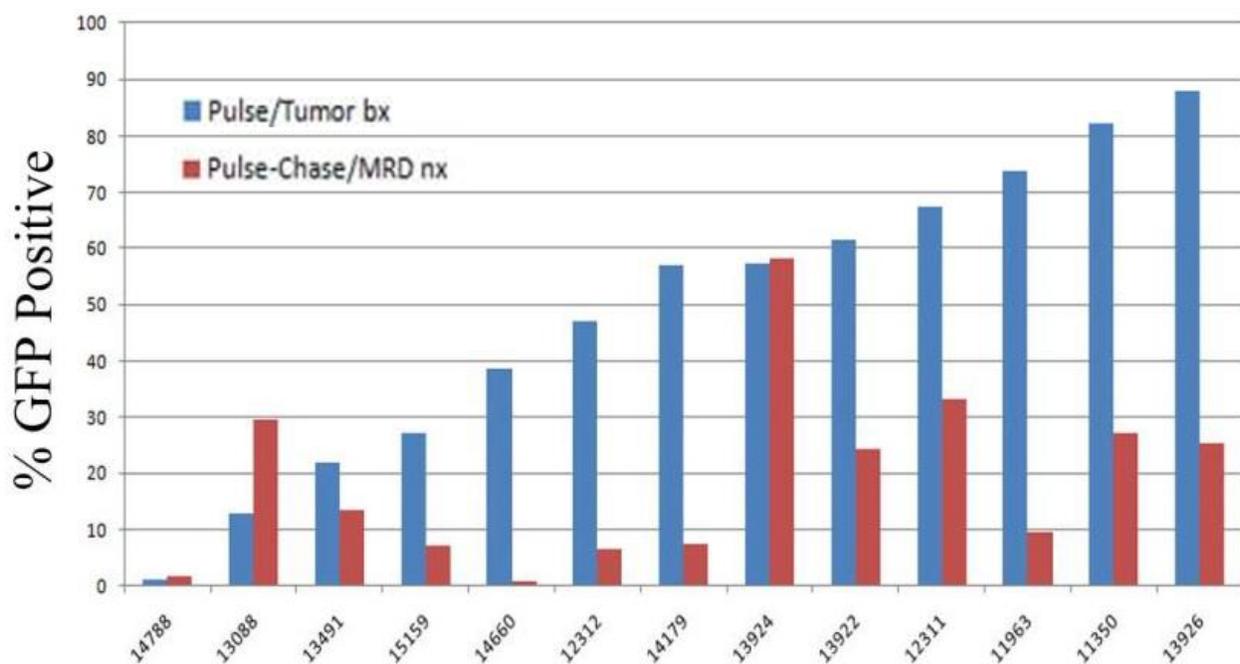


Figure 2. H2B-GFP labeled mammary tumors show variable H2B-GFP label retention within MRD lesions. Graph depicts flow cytometry-based GFP positivity measurements performed on thirteen paired mammary tumor biopsy-necropsy (tumor-MRD) samples. Blue bars depict the % GFP positive cells detected in tumor biopsy samples collected during ongoing Dox treatment. Magenta bars represent the % GFP positive cells detected in matched MRD lesions collected 6 to 8 weeks after Dox withdrawal. As before, a wide range of H2B-GFP labeling was observed during Dox treatment. In addition, the extent of H2B-GFP label retention within MRD was highly variable from lesion to lesion, suggesting variable proliferation-dependent washout of the H2B-GFP label.

**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  
 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. Tumor cell heterogeneity maintained by cooperating subclones in Wnt-driven mammary cancer	Cleary, A. S. Leonard, T. L. Gestl, S. A. Gunther, E. J.	Nature	July 2013	<input type="checkbox"/> Submitted <input type="checkbox"/> Accepted <input checked="" type="checkbox"/> Published

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

Yes \_\_\_\_\_ No   X  

If yes, please describe your plans:

**21. Changes in Outcome, Impact and Effectiveness Attributable to the Research Project.**

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

None

**22. Major Discoveries, New Drugs, and New Approaches for Prevention Diagnosis and Treatment.**

Describe major discoveries, new drugs, and new approaches for prevention, diagnosis and treatment that are attributable to the completed research project. If there were no major discoveries, drugs or approaches, insert “None”; do not use “Not applicable.” Responses must be single-spaced below, and no smaller than 12-point type. **DO NOT DELETE THESE INSTRUCTIONS.** There is no limit to the length of your response.

The major insight from this research project was that aspects of H2B-GFP labeling of Wnt mammary tumors appeared inconsistent with a hierarchical cellular configuration. This led us to consider an interclonal cooperation model for Wnt-driven mammary tumors which in turn led us to pursue the notion that a subset of Wnt tumors relies on cooperating subclones for tumor maintenance. We discovered that a subset of Wnt tumors is indeed comprised of cooperating subclones. This discovery has important implications for interpreting the subclonal diversity identified in breast cancer genome sequencing studies.

**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.

## BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Gunther, Edward J.	POSITION TITLE Associate Professor of Medicine		
eRA COMMONS USER NAME (credential, e.g., agency login) egunther			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
Hofstra University, Hempstead, NY	B.S.	/88	Chemistry
Yale University School of Medicine, New Haven, CT	M.D.	/93	Medicine
Hospital of the University of Pennsylvania, Philadelphia, PA	Medicine	/95	Medicine Residency
Hospital of the University of Pennsylvania, Philadelphia, PA	Oncology	/99	Oncology Fellowship

### A. Personal Statement

Dr. Gunther is a physician-scientist and practicing Medical Oncologist with more than 14 years of breast cancer research experience. His primary mission within the Penn State Cancer Institute involves directing an NCI-funded research laboratory devoted to developing and analyzing novel genetically engineered mouse models of breast cancer (85% research effort). The long-range goal of the Gunther lab is to use these models to elucidate molecular and cellular mechanisms of breast carcinogenesis and tumor maintenance.

The Gunther lab is committed to providing a training environment for launching careers in breast cancer research. Current trainees in the Gunther laboratory include one student performing thesis research toward an M.D.-Ph.D. combined degree and one student performing thesis research toward the Ph.D. degree. Three Gunther lab trainees have successfully competed for pre-doctoral fellowships through the Department of Defense Breast Cancer Research Program.

### B. Positions and Honors

#### Positions and Employment

1989	Medical Student Summer Research Fellowship, Yale University School of Medicine (Laboratory of Dr. Richard Flavell), New Haven, CT
1991-1993	Medical Student Research Fellowship, Yale University School of Medicine (Laboratory of Dr. Peter Glazer), New Haven, CT
1993-1994	Intern, Department of Internal Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA
1994-1995	Resident, Department of Internal Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA
1995-1999	Research/Clinical Fellow, Department of Oncology, University of Pennsylvania, Philadelphia, PA
1996-2002	Postdoctoral Resident Fellow, University of Pennsylvania, Philadelphia, PA (Laboratory of Dr. Lewis Chososh)

- 2002-2008 Assistant Professor, Department of Medicine, Pennsylvania State College of Medicine, Hershey, PA
- 2008-present Associate Professor of Medicine, Pennsylvania State College of Medicine, Hershey, PA

### Honors

- 1988 American Chemical Society Award, Hofstra University
- 1988 Phi Beta Kappa, Hofstra University
- 1988 Highest Honors in Chemistry, Hofstra University (undergraduate research)
- 1992 Farr Scholar Award, Yale School of Medicine
- 1993 Nicholas Giarmar Prize, Yale School of Medicine (M.D. thesis research, Yale)
- 1995 Humaneness in Medicine Award for Housestaff (Pennsylvania Medical Society)
- 1997 Diplomate in Internal Medicine, American Board of Internal Medicine
- 2000 Diplomate in Medical Oncology, American Board of Internal Medicine

### **C. Selected Peer-reviewed Publications** (Selected from 23 peer-reviewed publications)

1. **Gunther EJ**, Yeasky TM, Gasparro FP, Glazer PM. Mutagenesis by 8-methoxypsoralen and 5-methylangelecin photoadducts in mouse fibroblasts: mutations at cross-linkable sites induced by offoadducts as well as cross-links. *Cancer Res.* 1995 March 15; 55(6):1283-8.
2. D'Cruz CM, **Gunther EJ**, Boxer RB, Hartman JL, Sintasath L, Moody SE, Cox JD, Ha SI, Belka GK, Golant A, Cardiff RD, Chodosh LA. c-MYC induces mammary tumorigenesis by means of a preferred pathway involving spontaneous Kras2 mutations. *Nat Med.* 2001 Feb; 7(2):235-9.
3. **Gunther EJ**, Belka GK, Wertheim GB, Wang J, Hartman JL, Boxer RB, Chodosh LA. A novel doxycycline-inducible system for the transgenic analysis of mammary gland biology. *FASEB J.* 2002 Mar; 16(3):283-92.
4. Moody SE, Sarkisian CJ, Hahn KT, **Gunther EJ**, Pickup S, Dugan KD, Innocent N, Cardiff RD, Schnall MD, Chodosh LA. Conditional activation of Neu in the mammary epithelium of transgenic mice results in reversible pulmonary metastasis. *Cancer Cell.* 2002 Dec; 2(6):451-61.
5. **Gunther EJ**, Moody SE, Belka GK, Hahn KT, Innocent N, Dugan KD, Cardiff RD, Chodosh LA. Impact of p53 loss on reversal and recurrence of conditional Wnt-induced tumorigenesis. *Genes Dev.* 2003 Feb 15; 17(4):488-501. PMID: PMC195997.
6. Frech MS, Halama ED, Tilli MT, Singh B, **Gunther EJ**, Chodosh LA, Flaws JA, Furth PA. Deregulated estrogen receptor alpha expression in mammary epithelial cells of transgenic mice results in the development of ductal carcinoma in situ. *Cancer Res.* 2005 Feb 1; 65(3):681-5.
7. Vargo-Gogola T, Heckman BM, **Gunther EJ**, Chodosh LA, Rosen JM. P190-B Rho GTPase-Activating Protein Overexpression Disrupts Ductal Morphogenesis and Induces Hyperplastic Lesions in the Developing Mammary Gland. *Mol Endocrinol.* 2006 Jun; 20(6):1391-405.
8. Shen Q, Zhang Y, Uray IP, Hill JL, Kim HT, Lu C, Young MR, **Gunther EJ**, Hilsenbeck SG, Chodosh LA, Colburn NH, Brown PH. The AP-1 transcription factor regulates postnatal mammary gland development. *Dev Biol.* 2006 Jul 15; 295(2): 589-603.
9. Jones RA, Campbell CI, **Gunther EJ**, Chodosh LA, Petrik JJ, Khokha R, Moorehead RA. Transgenic overexpression of IGF-IR disrupts mammary ductal morphogenesis and induces tumor formation. *Oncogene.* 2007 Mar 8; 26(11):1636-44.
10. Gestl SA, Leonard TL, Biddle JL, Debies MT, **Gunther EJ**. Dormant Wnt-initiated mammary cancer can participate in reconstituting functional mammary glands. *Mol Cell Biol.* 2007 Jan; 27(1):195-207. PMID: PMC1800647.

11. Debies MT, Gestl SA, Mathers JL, Mikse OR, Leonard TL, Moody SE, Chodosh LA, Cardiff RD, **Gunther EJ**. Tumor escape in a Wnt1-dependent mouse breast cancer model is enabled by p19/p53 pathway lesions but not p16 loss. *J Clin Invest*. 2008 Jan; 118(1):51-63. PMID: PMC2104482.
12. McHenry PR, Sears JC, Herrick MP, Chang P, Heckman-Stoddard BM, Rybarczyk M, Chodosh LA, **Gunther EJ**, Hilsenbeck SG, Rosen JM, Vargo-Gogola T. P190B RhoGAP has pro-tumorigenic functions during MMTV-Neu mammary tumorigenesis and metastasis. *Breast Cancer Res*. 2010 Sep; 12(5): R73
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14. Plichta KA, Mathers JL, Gestl SA, Glick AB, **Gunther EJ**. Basal but not luminal mammary epithelial cells require PI3K/mTOR signaling for Ras-driven overgrowth. *Cancer Res*. 2012 Nov 15;72(22):5856-66. PMID 23010075.
15. Cleary AS, Leonard, TL, Gestl, SA, **Gunther, EJ**. Tumor cell heterogeneity maintained by cooperating subclones in Wnt-driven mammary cancer. *Nature*. (in Press, PMID/PMCID pending).

## D. Research Support

### Ongoing Research Support

1 R01 CA152222-01 (Gunther, PI) 07/01/10 – 06/30/15  
 NIH/NCI  
 “Modeling Breast Cancer Relapse Prevention in Mice”  
 The major goal of this project is to identify molecular and cellular mechanisms that maintain breast cancer dormancy using genetically engineered mouse models.  
 Role: PI

W81XWH-09-1-0123 (Cleary, PI) 09/30/10 – 09/29/13  
 DOD Predoctoral Award  
 “Dissecting Epithelial Cell Interactions and Interclonal Cooperation During Mammary Tumorigenesis”  
 The major goal of this project is to oversee the research training of an MD-PhD combined degree candidate as she pursues insights into mechanisms of tumor cell clone-clone cooperativity during the growth and progression of mouse mammary cancers.  
 Role: Mentor

### Completed Research Support

Cancer Research Foundation Award 09/30/11 – 9/29/12  
 The Donald B. and Dorothy L. Stabler Foundation  
 “Discovery of Genes That Drive the Spread of Breast Cancer Using Mouse Models”  
 The major goal of this project is to use transposon-based discovery tools to uncover novel genes contributing to tumor cell dissemination in mouse models of breast cancer.  
 Role: PI

Tobacco Settlement Block Grant 9/01/11 – 8/30/12  
 “Interrogating the Role of Myoepithelial Cells in Mammary Carcinogenesis”

The major goal of this project is to use cell ablation strategies to define how mammary myoepithelial cells promote and/or inhibit mammary carcinogenesis in genetically engineered mouse models.

Role: PI

W81XWH-09-1-0123 (Plichta, PI)

01/15/09 – 01/14/12

DOD Predoctoral Award

“Compartment-specific Analysis of Mammary Epithelial Cell Transformation and Tumorigenesis”

Role: Mentor

5 R01 CA114001-04 (Gunther, PI)

9/30/05 - 7/31/10

NIH/NCI

“Preclinical Modeling of Latent Breast Cancer in Mice”

The major goal of this project is to elucidate genetic determinants of treatment sensitivity for dormant breast cancer using novel mouse models of latent mammary cancer at local and metastatic disease sites.

Role: PI

Translational Breast Cancer Research Award

07/01/10 – 06/30/12

The Mary Kay Foundation

“Dissecting Mammary Cell Lineage-Specific Signaling Pathway Dependencies in Breast Cancer”

The major goal of this project is to express oncogenic transgenes in the mouse mammary gland in a compartment-restricted manner to reveal how mammary cell subtype influences transformation.

Tobacco Settlement Block Grant (Smith, PI) 2003 – 2006

“Manipulation of Signaling Pathways for the Treatment of Breast Cancer”

The major goals of this project are to support a pool of dedicated professional researchers, i.e., postdocs who will conduct the studies and “encourage” new postdocs to submit applications for individual postdoctoral fellowships.

Role: Co-PI – Project 7

K08 CA 079682 (Gunther, PI)

09/01/99 – 08/31/04

NIH/NCI

“BRCA1 Function Using an Inducible Transgene”

Role: PI