Final Progress Report for Research Projects Funded by Health Research Grants

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

1. **Grantee Institution:** The Fox Chase Cancer Center

2. **Reporting Period (start and end date of grant award period):** 1/1/2009 – 12/31/2011

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

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

5. **Grant SAP Number:** 4100047634

6. **Project Number and Title of Research Project:** 3 – The ARF Tumor Suppressor aqnd Autophagy

7. **Start and End Date of Research Project:** 1/1/2009 – 12/31/2011

8. **Name of Principal Investigator for the Research Project:** Maureen Murphy, Ph.D.

9. **Research Project Expenses**.

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

   $510,222.06

   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	Position Title	% of Effort on Project	Cost

Murphy	PI	30% - YR01-03	$44,650.90
Pimkina	Graduate Student	50% - YR01	$8,679.88
Frank	Graduate Student	25% - YR01	$5,046
Budina	Graduate Student	50% - YR02	$11,874.93

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
Hontz	Postdoctoral Associate	100% YR01

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
Agilent QPCR machine, Mx3005P	This machine does quantitative assessment of the level of mRNA in a sample, in 96 well format. This machine was used for all aims of the proposed research, and its purchase significantly saved money spent using the Real-time PCR Core Facility at FCCC. As with all major equipment in the Murphy laboratory, this equipment became common use for the 2nd floor of the West building, and was frequently used by the Sigal and Kolenko laboratories. Additionally, these three laboratories shared the reagents for this machine that came free with its purchase (SYBR Green).	$25,610.67
Eppendorf Refrigerated micro-centrifuge	This machine is a high-speed microcentrifuge for the processing of DNA and RNA samples; it was purchased to	$4,362.96

	replace a 14-year old unit that had broken down. It was used for all aims of the proposed research.	

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

Yes_____ No____X_____

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

11. Leveraging of Additional Funds

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

Yes____X____ No_____

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

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

A. Title of research project on grant application	B. Funding agency (check those that apply)	C. Month and Year Submitted	D. Amount of funds requested:	E. Amount of funds to be awarded:
Heat shock protein 70 and cancer	☑ NIH ☐ Other federal (specify:_____ _____) ☐ Nonfederal	November 2010	$794,979	not funded (26th percentile)

	source (specify: _____)			
The ARF tumor suppressor	☑ NIH ☐ Other federal (specify:_____ _____) ☐ Nonfederal source (specify: _____)	March 2009	$2,181,250	$1,810,440
	☐NIH ☐ Other federal (specify:_____ _____) ☐ Nonfederal source (specify: _____)		$	$

Our R01 application "The ARF tumor suppressor" was originally submitted in 2008 and resubmitted in 2009. Overall our studies on ARF, autophagy and tumor survival were considered by the Reviewers of the initial application to be an "important and timely area of study with high translational potential". Strengths of the application were the "intriguing body of preliminary data", the "novelty of the hypothesis", and that the proposed experiments were "well-planned, well-controlled, and statistical treatment of data and alternate approaches fully considered". However, the Reviewers were concerned that much of the data presented in the application was unpublished at the time of initial submission.

Support from the PA DOH enabled us to complete these promising studies on the role of ARF in autophagy, and to publish 3 manuscripts directly related to the goals of the R01. Additionally, support from the DOH allowed us to generate seven new figures of preliminary data for the R01 related to the ability of ARF to traffic to mitochondria, using the support from the Electron Microscopy Core Facility at FCCC. These factors contributed heavily to the successful funding of the R01 in the next round of review. They also laid the groundwork for our identification of amino acids 120-169 as necessary for ARF's autophagy function.

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 am now submitting this work as a PI on a project on a P01 application for melanoma (BRAF inhibitors and melanoma, PI Herlyn, M) as well as a Leukemia/Lymphoma Society Translational Research Program grant, due March 1, 2012.

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

The goal of this project is to develop a promising new cancer cure, an HSP70 inhibitor that we call PAS. This continues to be the goal, and we fully expect PAS to enter clinical trials in the next 5-7 years.

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			3	
Unknown				
Total			**3**	

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

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

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 solidified a collaboration between my group and those of Roland Dunbrack and Tim Yen, both experts in molecular modeling and cell cycle checkpoints, respectively, at the Fox Chase Cancer Center. It utilized the services of the Organic Synthesis Facility at Fox Chase. The compound, PAS, was patented as a novel anti-cancer compound, in a joint patent between The University of Pennsylvania and FCCC.

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____X_____ No_____

If yes, please describe the collaborations:

Donna L. George, University of Pennsylvania School of Medicine
Jeffrey Barrett, Children's Hospital of Philadelphia (to study PAS efficacy in childhood ALL)
Gwenn Danet-Desnoyers, University of Pennsylvania School of Medicine (to perform xenograft assays with patient ALL samples)

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

Yes___X_____ No_____

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

This compound was patented as a novel anti-cancer agent.

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

Yes_____ No____X_____

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

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

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

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

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

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

Specific aims:

Aim 1. To define the domains of ARF necessary for mitochondrial localization, autophagy induction, and interaction with Hsp70.

Aim 2. To evaluate the efficacy of a novel Hsp70 inhibitor (PAS) to kill human tumor cell lines.

Aim 3. To test the hypothesis that ARF and Hsp70 silencing are inhibitory to human tumor development in a xenograft model.

Progress:

ARF, mitochondria and autophagy.

The p14/p19ARF (ARF) tumor suppressor gene is frequently mutated in human cancer. We and others had shown that ARF could localize to mitochondria and to induce autophagy. However,

the controls that regulate the trafficking of ARF to mitochondria remained unknown. We reported that 2-phenylacetylsulfonamide (PAS) selectively interacts with cytosolic heat shock protein 70 (HSP70) and inhibits its function; we further showed that PAS promotes the death of tumor cells, and that this is associated with an impairment of lysosome function and an inhibition of autophagy. We used a mass spectrometry-based approach to identify mitochondrial ARF-binding proteins, and found that mitochondrial ARF interacts with HSP70. We showed that treatment of cells with PAS blocks the trafficking of ARF to mitochondria, indicating that interaction with HSP70 mediates the mitochondrial localization of ARF. We also showed that PAS inhibits the ability of ARF to induce autophagy, supporting the premise that localization to this organelle is critical for ARF-induced autophagy. Finally, we found that cells expressing high levels of ARF are more sensitive to PAS than counterparts with ARF silenced. As high levels of ARF are characteristic of tumor cells with mutant p53, as well as enhanced MAPK signaling and advanced stage, our data supported the premise that PAS may show preferential cytotoxicity to advanced stage cancers. These findings were published in Pimkina and Murphy, Can Biol Ther, and were used as a foundation to successfully procure R01 funding in 2010.

In a manuscript in preparation, we identified the domains of ARF that are required for its mitochondrial localization (amino acids 1-50) as well as its autophagy function (amino acids 120-169). In this work, we were able to reconcile some disparate research in the literature concerning the role of ARF in autophagy. Specifically, using inducible cell for different ARF mutants, we were able to show that full-length ARF is capable of inducing both autophagy and mitophagy (selective degradation of mitochondria); the latter function likely explains the requirement for ARF localization to mitochondria for its autophagy function. We were able to conclude that the small molecular weight version of ARF called smARF does not induce, but rather inhibits, autophagy and mitophagy. Finally, we were able to indentify a novel domain in ARF, from amino acids 120-169, which is highly conserved and also subject to mutations in human cancer, as the key autophagy domain of ARF.

Mechanisms of action of the HSP70 inhibitor 2-phenylacetylsulfonamide (PAS, or PES).

The evolutionarily conserved stress-inducible HSP70 molecular chaperone plays a central role in maintaining protein quality control in response to various forms of stress. Constitutively elevated HSP70 expression is a characteristic of many tumor cells and contributes to their survival. We identified the small molecule 2-phenylacetylsulfonamide (PAS, also called PES) as a novel HSP70 inhibitor. We first identified PAS as a compound that inhibits autophagy. However, because HSP70 works closely with the HSP90 molecular chaperone, we also tested the hypothesis that PAS function similarly to an HSP90 inhibitor. Indeed, we found that treatment of cancer cells with PAS results in an impairment of the two major protein degradation systems, namely, the autophagy-lysosome system and the proteasome pathway. As a consequence, many cellular proteins, including known HSP70/HSP90 substrates, accumulate in detergent-insoluble cell fractions, indicative of aggregation and functional inactivation. Overall, PAS simultaneously disrupts several cancer critical survival pathways, supporting the idea of targeting HSP70 as a potential approach for cancer therapeutics. These findings support the premise that PAS should be developed further as an anti-cancer modality. This manuscript was published in Mol Can Res in 2011, and it serves as the foundation for our submission of a Leukemia Lymphoma Society Translational Research Program application in March 2012.

Identification and characterization of a unique analogue of PAS, PAS-Cl.

We reported that PAS binds and inhibits the major cytosolic form of the stress-induced chaperone HSP70. In a manuscript in preparation, we tested several derivatives of PAS and noted that one, which we call PAS-Cl, has 10-fold improved toxicity to tumor cells. Notably, this compound showed nanomolar efficacy in melanoma tumors, but primary melanocytes were resistant to toxicity, using the MTT assay. PAS-Cl also showed markedly improved efficacy in a mouse model of Burkitts lymphoma. We found that PAS-Cl has enhanced ability to inhibit autophagy and induce cell death in tumor cells. Treatment of cells also results in G2/M arrest, and along with Tim Yen at Fox Chase Cancer Center, we found that this compound activates a G2/M checkpoint in tumor cells. In collaboration with Roland Dunbrack at Fox Chase Cancer Center, we used in silico docking to identify potential binding sites for PAS on HSP70. We identified several, and then used site-directed mutagenesis of predicted key contact residues and identified three mutants of HSP70 that fail to bind PAS. Notably, all three of these residues map to one potential docking site of PAS. This manuscript is about to be submitted as a priority report to Cancer Research. We are currently collaborating with Ronen Marmorstein at the Wistar Institute to crystallize the C terminus of HSP70 with PAS. We are likewise collaborating with Dr. Jeffrey Barrett at Children's Hospital of Philadelphia and Dr. Gwenn Danet-Desnoyers at the University of Pennsylvania School of Medicine to test the efficacy of PAS in childhood and adult ALL and AML, transplanted into animal models, and to uncover the pharmacokinetics and pharmacodynamics of PAS. These steps are necessary to transition PAS closer to human clinical trials.

Whereas we were not successful obtaining R01 support for our findings on PAS (26th percentile), we are submitting this project as part of a P01 application on melanoma at the Wistar Institute. In sum, the goals of this application from the PA DOH have been met: this work led to three manuscripts in press, two to be submitted, four collaborative efforts with other Philadelphia scientists, and one successful R01.

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, 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-	Month and	Publication

		reviewed Publication:	Year Submitted:	Status (check appropriate box below):
1. HSP70 Inhibition by the Small-Molecule 2-Phenylethynesulfonamide Impairs Protein Clearance Pathways in Tumor Cells	J. I-Ju Leu, Julia Pimkina, Pooja Pandey, Maureen E. Murphy, and Donna L. George	Molecular Cancer Research	Jan 2011	☐Submitted ☐Accepted ☑ Published
2. Interaction of the ARF tumor suppressor with cytosolic HSP70 contributes to its autophagy function	Julia Pimkina and Maureen E. Murphy	Cancer Biology and Therapy	Feb 2011	☐Submitted ☐Accepted ☑ Published
3. p53 and ARF: unexpected players in autophagy	Gregor M. Balaburski, Robert D. Hontz and Maureen E. Murphy	Trends in Cell Biology	Sept 2010	☐Submitted ☐Accepted ☑ Published

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

Yes___X_____ No_____

If yes, please describe your plans:

We are finished with a collaborative effort between my lab and that of Roland Dunbrack, and Tim Yen, both of Fox Chase Cancer Center. This manuscript "An HSP70 inhibitor induces a mitotic checkpoint in tumor cells and shows pre-clinical efficacy in a murine model of lymphoma" will be submitted as a Priority report to Cancer Research in March 2012.

We are also 3-6 months from submitting a manuscript on Aim 1, where we identify a novel domain in the ARF tumor suppressor that plays a role in autophagy. This manuscript will be submitted to J Biol Chem.

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.

Funds from this mechanism have allowed for the progression of a highly novel cancer therapy from cell line assays to pre-clinical models, where this compound has shown remarkable efficacy.

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.

PAS-Cl, a derivative of PAS, is a major new drug with pre-clinical efficacy in a mouse model of lymphoma.

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__X_____ 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: Modulators of HSP70/DNAK function and Methods of Use Thereof , patent 13/051,511
b. Name of Inventor(s): Julia I-Ju Leu, Donna L. George, Maureen E. Murphy

c. Technical Description of Invention (describe nature, purpose, operation and physical, chemical, biological or electrical characteristics of the invention):
   A novel HSP70 inhibitor for cancer therapy, useful because it inhibits a cancer-critical survival pathway, autophagy

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_____X_____ No____

   If yes, indicate date patent was filed: 12/2009, amended 6/2011

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____X
   If yes, indicate number of patent, title and date issued:
   Patent number:

Title of patent:

f. Were any licenses granted for the patent obtained as a result of work performed under this health research grant? Yes_____ No X__

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 X__

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____X_____ No_____

If yes, please describe your plans:

I fully expect to complete the pharmacokinetics and toxicity studies in mouse, such that PAS will be licensed by major pharmaceuticals.

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.*

Biosketch included for Dr. Murphy

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.**

NAME	POSITION TITLE
Maureen E. Murphy, Ph.D.	Professor
eRA COMMONS USER NAME MMurphy	

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)*	YEAR(s)	FIELD OF STUDY
Rutgers University, New Brunswick, NJ	B.Sc.	1982-5/1987	Biochemistry
University of Pennsylvania School of Philadelphia, PA	Ph.D.	1987-12/1993	Molecular Biology
Princeton University, Princeton, NJ	Postdoctoral	1994-1998	

A. PERSONAL STATEMENT

I have over twenty years of experience on the biochemistry and molecular biology of cancer. For the past fourteen years I have maintained a continuously-NIH-funded program focused on the p53 and ARF tumor suppressor proteins and their roles in apoptosis and autophagy, respectively. This work includes the creation of mouse models of polymorphic variants of p53, as well as the elucidation of the function of ARF and HSP70 in autophagy. The goal that has pervaded my work has been to conduct research aimed toward improved treatment of cancer.

B. POSITIONS AND HONORS

Pre-doctoral trainee, University of Pennsylvania School of Medicine 1987-1993
Post-doctoral Fellow, Princeton University, Princeton, NJ 1994-1998
Assistant Professor, Fox Chase Cancer Center, Philadelphia, PA 1998-2003
Associate Professor with tenure, Fox Chase Cancer Center 2003-date
Adjunct Professor, Drexel University School of Medicine, Philadelphia, PA 2004-2011
Director, Postdoctoral Training Program, Fox Chase Cancer Center 2005-2011
Co-Director, NIH NCI Training Grant, Training Program in Cancer Research 2005-2011
Professor, Fox Chase Cancer Center 2011
Professor and Leader, Molecular and Cellular Oncogenesis, The Wistar Institute 2011-date
Associate Director of Faculty Development, The Wistar Institute 2011-date

HONORS AND AWARDS

George H. Cook Scholar (1987); Pre-doctoral training grant, University of Pennsylvania (NIH T32-GM07229; 1989-1991); Jane Coffin Childs Memorial Fund Fellowship (1994-1997); W.W. Smith Charitable Trust Foundation Award (1998-2000); ACS New Investigator Pilot Award (1999); Invited Speaker, International p53 Workshop (2004, 2008, 2010); Guest Editor, Oncogene "Polymorphisms and Cancer" (2006); Co-Organizer, 15th International p53 Workshop (2010); Basic Science Award Selection Committee, AACR (2011); Carcinogenesis Award Selection Committee (2011).

EDITORIAL BOARDS, MEMBERSHIPS, PEER REVIEW

Member, American Association for Cancer Research (1999-date); Member, NIH NCI Study Section, Cancer Manpower and Training (NCI-F) (1999-2003); Member, NIH NCI Study Section, Tumor Cell Biology (TCB) (2004-2006); Member, NIH NCI Study Section, Molecular

Oncogenesis (MONC) (2006-2008); Associate Editor, *Cancer Research* (2005-date); Associate Editor, *Carcinogenesis* (2009-date); Associate Editor, *Journal of Clinical Investigation* (2009-2012).

C. SELECTED PEER-REVIEWED PUBLICATIONS (from a total of 45)

Dumont, P., Leu, J.I., Della Pietra, A.C., George, D.L., **Murphy, M.** The codon 72 polymorphic variants of p53 demonstrate markedly different apoptotic potential. *Nature Genetics* **33**:357-365, 2003.

Leu, J.I., Dumont, P., Hafey, M., **Murphy, M.E.**, George, D.L. Mitochondrial p53 activates BAK and leads to disruption of a BAK/MCL1 complex. *Nat. Cell Biol.* **6**:443-450, 2004.

Lin, T., Chao, C., Saito, S., Mazur, S.J., **Murphy, M.E.**, Appella, E., Xu, Y. p53 induces differentiation of mouse embryonic stem cells by suppressing Nanog expression. *Nat. Cell Biol*. **7**:165-171, 2005.

Li, X., Dumont, P., Della Pietra, A.C., Shetler, C., **Murphy, M.E.** The codon 47 polymorphism in p53 is functionally significant. *J. Biol. Chem.* **280**:24245-24251, 2005.

Pietsch, E.C., Leu, J.I., Frank, A., Dumont, P., George, D.L., **Murphy, M.E.** The tetramerization domain of p53 is required for efficient BAK oligomerization. *Cancer Biol. Ther*. **6**:1576-1583, 2007.

Pietsch, E.C., Perchiniak, E., Canutescu, A.A., Wang, G., Dunbrack, R.L., **Murphy, M.E.** Oligomerization of BAK by p53 utilizes conserved residues of the p53 DNA binding domain. *J. Biol. Chem*. **283**:21294-21304, 2008.

Humbey, O., Pimkina, J., Zilfou, J.T., Jarnik, M., Dominguez-Brauer, C., Burgess, D.J., Eischen, C.M., **Murphy, M.E.** The ARF tumor suppressor can promote the progression of some tumors. *Cancer Res*. **68**:9608-9613, 2008.

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D. RESEARCH SUPPORT

R01 CA102184 (PI: Murphy) 06/01/2005 – 12/31/2014. Role: Principal Investigator
Functional Analysis of p53 Polymorphic Variants

R01 CA139319 (PI:Murphy) 01/01/2010 – 12/31/2014 Role: Principal Investigator
The ARF tumor suppressor