

# 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 Pennsylvania State University
2. **Reporting Period (start and end date of grant award period):** 1/1/2009 – 12/31/2012
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:** # 4100047645
6. **Project Number and Title of Research Project:** 16 - P16 Alteration and BRAF Mutation and Patient Outcomes in Papillary Thyroid Cancer
7. **Start and End Date of Research Project:** 5/01/2009 - 06/30/2011
8. **Name of Principal Investigator for the Research Project:** David Goldenberg, MD, FACS
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:

\$ 61,973

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
Steele	Technician	2010-2011 8%	8,819
Choby	Medical Student	2009-2010 1%	220
Chandagalu-Doer	Technician	2009-2010 60%	28,804

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
Goldenberg	Principal Investigator	3%
Robertson	Co-Principal Investigator	2%
Durvesh	Co-Investigator	5%
Crist	Co-Investigator	1%
Manni	Co-Investigator	2%
Mauger	Statistician	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 \_\_\_\_\_ No X \_\_\_\_\_

If yes, please describe your plans:

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

This project was completed in June 2011 and results were presented at the International Head and Neck Cancer Meeting- Toronto 2012.

**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 \_\_\_\_\_ Yes 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 supported collaborative studies among investigators in the Departments of Surgery, Medicine/Endocrinology, Pathology, Pharmacology and Public Health Sciences.

**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 application’s strategic plan). Summarize the progress made in achieving these goals, objectives and aims for the entire grant award period. 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 (□) and include the appropriate citation(s). DO NOT DELETE THESE INSTRUCTIONS.**

### Introduction:

Thyroid cancer represents the most common endocrine malignancy, with papillary thyroid cancer (PTC) accounting for 90% of malignant thyroid tumors. Although, outcome is generally favorable, a group of patients develops local recurrence and/or distant metastases. They stop responding to conventional treatment and ultimately die of their disease. It is for this group of patients with aggressive disease, that better diagnostic and prognostic tools are clearly needed to guide the treatment of individuals diagnosed with DTC (differentiated thyroid cancer). Molecular markers that accurately predict tumor behavior are lacking. In the past, p16 gene alterations and BRAF mutations have individually been implicated in tumor aggressiveness in PTC. We hypothesize that presence of these mutations simultaneously in patients with PTC is a predictor of worse clinical outcomes and tumor aggressiveness.

### Specific Aims:

Specific Aim 1. To analyze surgical specimens of Papillary Thyroid Cancer (PTC) for the presence of p16 alterations and BRAF mutations.

Specific Aim 2. To correlate the concurrent presence of p16 alterations and BRAF mutations (as outlined in specific aim 1) with patient outcomes as manifested by distant metastases, local recurrence and loss of iodine avidity.

### Research Design and Methods:

We conducted this retrospective study to analyze simultaneous presence of BRAF mutations and p16 alterations in cases of PTC and their correlation with worsening clinical outcomes. Prior to the Grant award period, we applied for and received IRB approval and PSCI Scientific review committee approval.

### Study Population:

Co-investigator (SD) collected thyroid tissue from 32 patients with PTC that underwent total thyroidectomy and / or central neck and / or lateral lymph node dissection, as necessary, at the Hershey Medical Center. Informed consent from donors was obtained through the PSCI Tissue Bank. The tissue samples were cryo frozen after surgery and then held in The Penn State Hershey Cancer Institute (PSHCI) Tissue Bank. Co-investigator (S.D) also collected 32 normal thyroid specimens from the Tissue bank (acting as control tissue). The human subjects and their specimens were protected with the use of a barcode and the key was kept only by the tissue bank coordinator.

### Procedures:

#### *BRAF Analysis:*

Tissue was allocated to the basic scientist, Co-PI (GR) for BRAF analysis. Tumors were either frozen or formalin fixed paraffin embedded sections. Frozen tumors were ground in a mortar and pestle and split in half. Formalin fixed paraffin embedded sections were dissolved in xylene and then rehydrated with 100% ethanol. Half of each frozen tumor was used as protein for western blot and half was used in Allele Specific PCR for BRaf<sup>V600E</sup> Mutation screening. DNA was extracted for ASPCR from both the frozen tumor halves and the formalin fixed paraffin embedded sections by way of the DNeasy<sup>®</sup> Blood and Tissue Kit (Qiagen). Extracted DNA was

amplified in a GeneAmp® PCR System 9700 (Applied Biosystems). 100ng DNA samples were mixed with Custom Premium Oligos primers for GAPDH and Mutant BRAf<sup>V600E</sup> (Invitrogen). Taq Polymerase was used in a premixed formula in Qiagen's Taq PCR Master Mix. Amplified DNA was run on a 2% Agarose gel at 100mV for 1 hour and imaged under UV light in an Alpha Innotech MultiImage™ Light Cabinet.

Protein expression levels were performed by western blot and then quantified using ImageJ software provided on the NIH website. Protein from tumors was quantified using the BCA Protein Quantification Kit. (Thermo Fisher) Protein was run on Invitrogen's 4-12% Bis Tris gradient acrylamide gels, and probed for phospho AKT, phosphoERK1/2, and  $\alpha$  enolase. (Cell Signaling and Santa Cruz) In assessing expression levels each tumor expression set was normalized for its  $\alpha$  enolase levels.

#### P16 Analysis:

IHC for p16 was performed using the CINtec p16 Histology kit (mtm Laboratories, Westborough, MA). FFPE sections were first deparaffinized and hydrated through xylenes and a graded ethanol series followed by heat-induced epitope retrieval in the CINtec unmasking solution for 20 minutes. This was followed by a 10 minute 3% peroxidase block at room temperature. Incubation with the p16 primary antibody was then performed at room temperature for 30 minutes followed by incubation with the CINtec Histology kit Visualization Reagent for 30 minutes at room temperature. Staining was completed with development of the kit's DAB chromagen substrate for 10 minutes followed by counterstaining for 6 minutes in Mayer's modified hematoxylin (Dako Cytomation, Carpinteria, CA). Sections were dehydrated, cleared and coverslipped.

P16 stained both the cytoplasmic and nuclei. It was scored as 3+ (>5% of the cells stain strongly positive), 2+ (<5% of the cells stain strongly but > 25% of the cells stain moderately positive), 1+ (1 < 5% of the cells stain strongly and 5 < 25% moderately positive, and 0 (< 1% of the cells stain strongly and < 5% stain moderately positive, or there is only weak or no staining). 3+ and 2+ were graded as positive, 1+ as weakly positive, and 0 as negative.

#### Clinical Correlations:

The Tissue Bank provided the human subjects' identifiers to the honest broker. Subsequently the honest broker reviewed the study subject's medical records to ascertain patients' extent of thyroid cancer and provided the de-identified clinical data to PI (DG) and Co-investigator (SD). Once the BRAF and p16 analysis was completed, the clinical investigators, that are the Co-PI (DG) and Co-investigators (SD) made the correlations between the presence of these markers and clinical outcomes.

#### Results:

##### Clinicopathological Data:

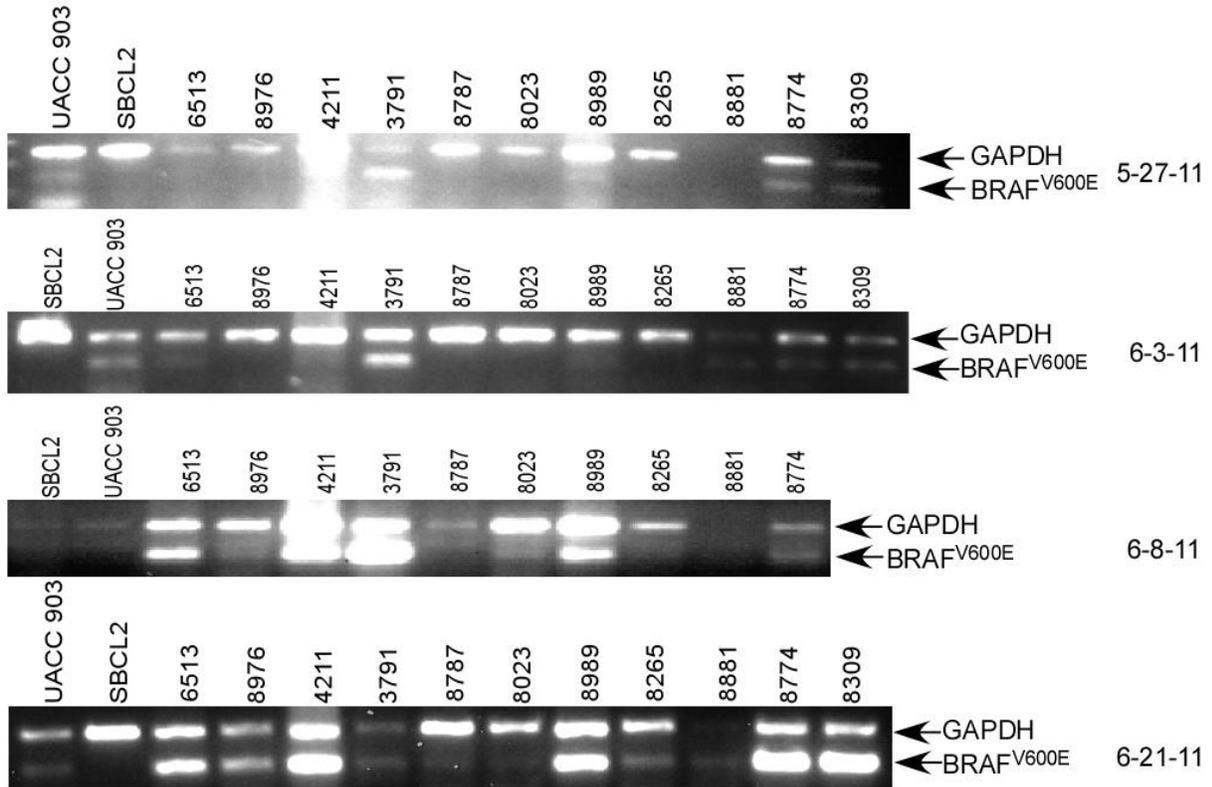
Over the Grant award period, 32 patients with PTC (10 men, 22 women) with a median age of 52 years (range 14-87 years) were recruited onto the study. Tumor and corresponding normal tissue samples from each patient were used as controls. The mean diameter of the PTCs was 1.65 cm (range 0.2 – 5.0 cm). The tumors were classified according to TNM staging to be Stage I in 70%

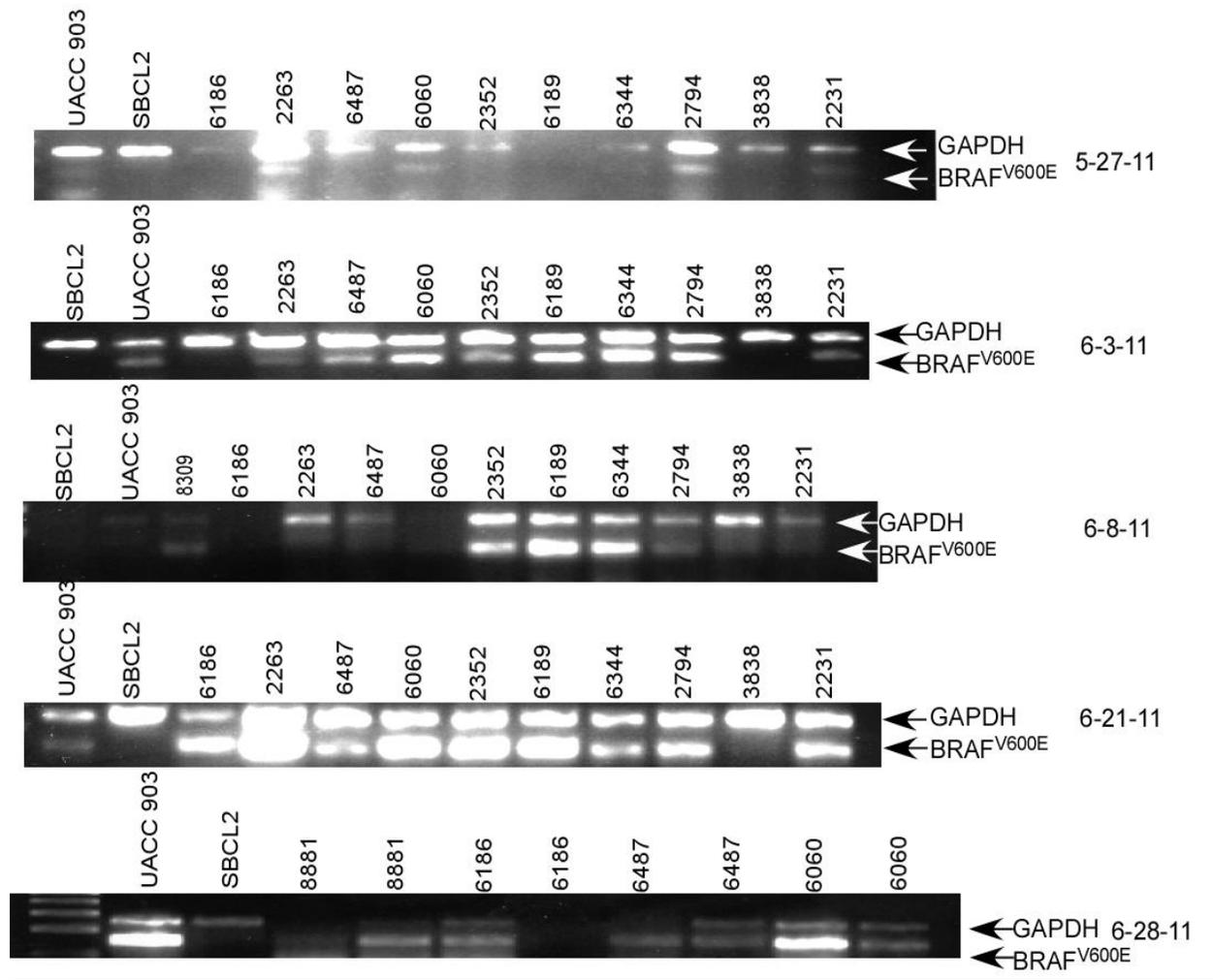
(n = 22), II in 12 % (n = 4) and IV in 16% (n = 5). Out of this cohort, one patient died of PTC, 5 patients were alive with recurrent disease.

**BRAF Mutations:**

As compared with previous reports of BRAF occurrence in 29-69% of patients with PTC [17-20], our series of PTC showed a high prevalence of *BRAF* mutation, 78 % (n = 25).

RAW DATA:





**Table 1.** Correlation between clinicopathological characteristics and BRAF mutation status in patients with PTC

	BRAF+	BRAF-	<i>P</i> value
n (total)	25	7	
Age at diagnosis (yr)	48 (14–86)	55 (20–83)	*
Gender, male	6	4	*
Tumor size (cm) <sup>2</sup>	2.1 (0.3–5.1)	1.38(0.2-2.5)	*
Multifocality <sup>1</sup>	7	4	*
Extrathyroidal invasion <sup>1</sup>	4	1	*
Lymph node metastasis <sup>1</sup>	9	2	*
Tumor stage <sup>1</sup>			
I	17	5	*
II	3	1	*
III	0	0	*
IV	3	1	*
Tumor recurrence <sup>1</sup>	4	1	*

1 In one sample that was BRAF positive these parameters were not recorded.

2 In two samples tumor size was not recorded

\* Pending

#### Immunohistochemical detection of p16:

In the literature, p16 overexpression has been described in 54-89% of patients with PTC [28, 29]. Consistent with these reports, in our series overexpression of p16 was detected in 78% (n = 25). P16 was negative in 21.88% (n = 7).

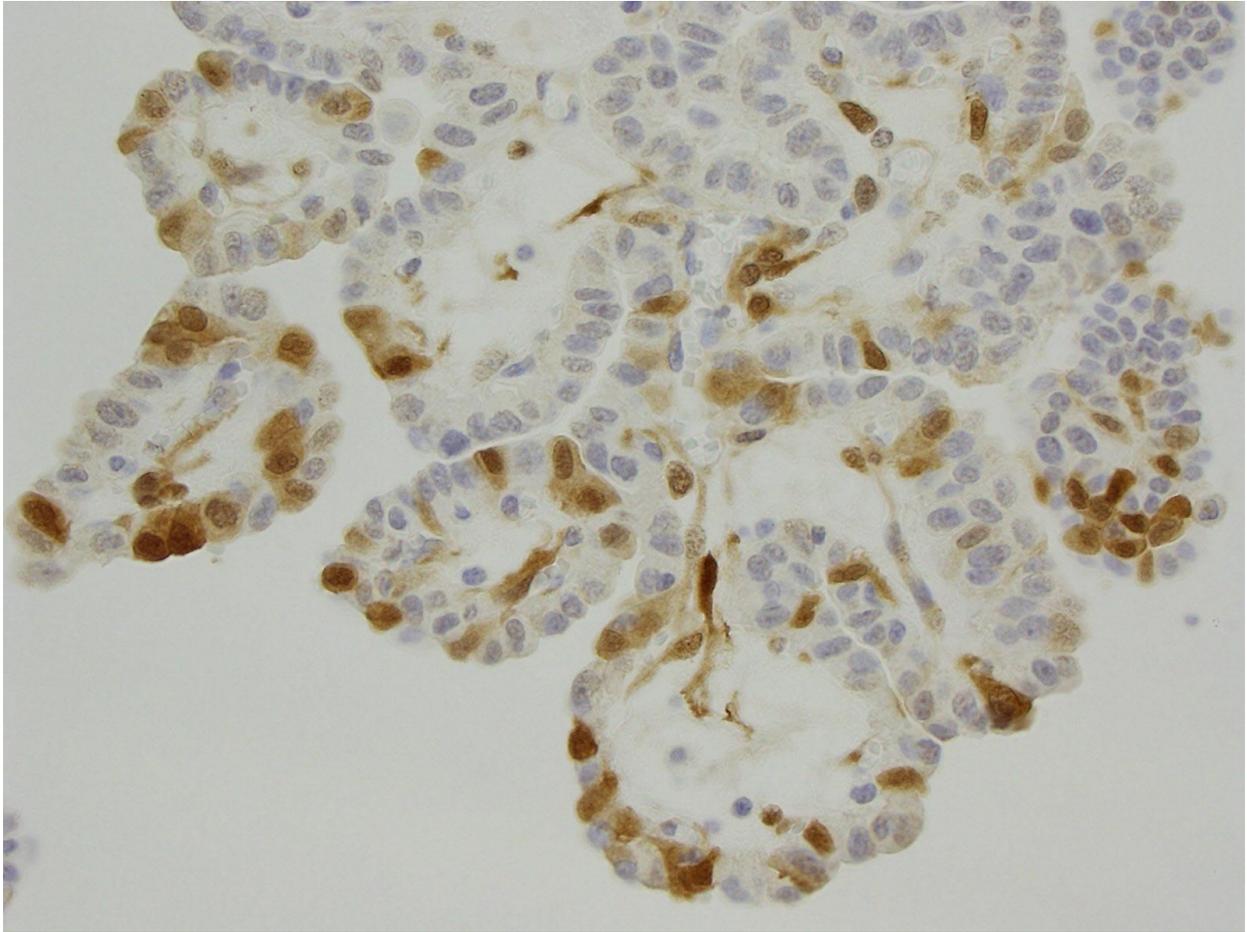


Figure 1.

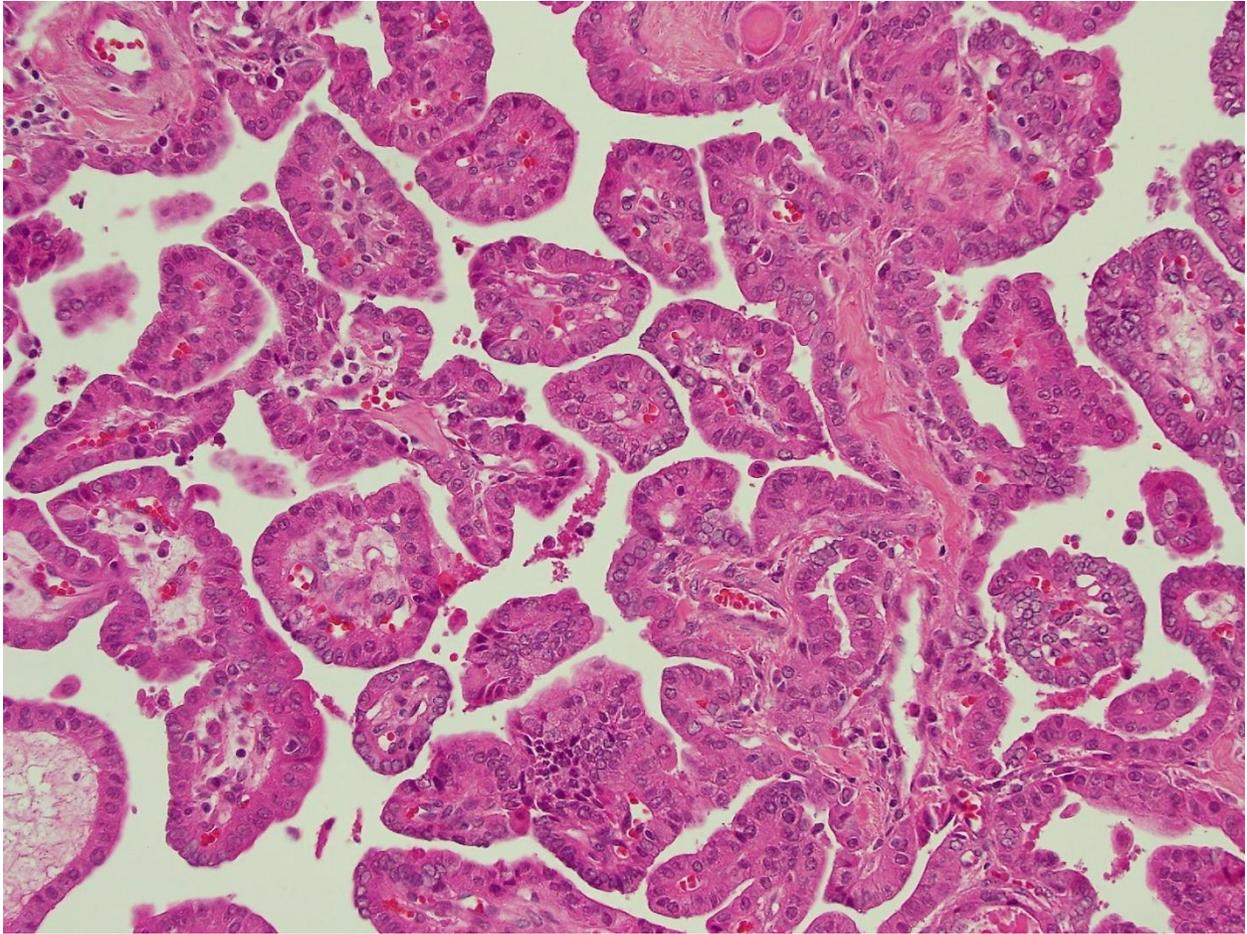


Figure 2.

**Table 2.** Correlation between clinicopathological characteristics and p16 overexpression in patients with PTC.

	P16+	P16–	<i>P</i> value
n (total)	25	7	*
Age at diagnosis (yr)	52 (14–87)	52 (18-70)	*
Gender, male	7	3	*
Tumor size (cm) <sup>2</sup>	1.85 (0.3–5.1)	1.7(0.2-3)	*
Multifocality <sup>1</sup>	8	3	*
Extrathyroidal invasion <sup>1</sup>	5	0	*
Lymph node metastasis <sup>1</sup>	9	2	*
Tumor stage <sup>1</sup>			
I	16	6	*
II	3	1	*
III	0	0	*
IV	5	0	*
Tumor recurrence <sup>1</sup>	5	1	*

1 In one sample that was p16 positive these parameters were not recorded.

2 In 2 samples tumor size was not recorded

\*Pending

#### Coexisting BRAF mutations and p16 alterations:

We expected concurrent presence of BRAF mutations and p16 alterations in at least 30% of our study subjects. Results indicated that coexisting BRAF mutations and p16 alterations were detected in 62.5% (n = 20) patients.

**Table 3.** Correlation between clinicopathological characteristics and co-existing p16 overexpression and BRAF mutations in patients with PTC.

	BRAF+	P16+	BRAF+ p16+
n (total)	25	25	20
Age at diagnosis (yr)	48 (14–86)	52 (14–87)	50 (14-87)
Gender, male	6	7	5
Tumor size (cm) <sup>2</sup>	2.1 (0.3–5.1)	1.85 (0.3–5.1)	1.9 (0.3-5.1)
Multifocality	7	8	5
Extrathyroidal invasion <sup>1</sup>	4	5	4
Lymph node metastasis <sup>1</sup>	9	9	7
Tumor stage <sup>1</sup>			
I	17	16	13
II	3	3	2
III	0	0	0
IV	3	5	4
Tumor recurrence <sup>1</sup>	4	5	4

<sup>1</sup>In one sample with concurrent presence of p16 overexpression and BRAF mutation these parameters were not recorded.

<sup>2</sup>In two samples tumor size was not recorded

\*P value for the above Pending statistical analysis.

## F. LITERATURE CITED:

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4. American Cancer Society. Cancer facts and figures 2007. <http://www.cancer.org/downloads/STT/CAFF2007PWSecured.pdf>.
5. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002. *JAMA.* May 10 2006;295(18):2164-2167.
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**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, listed in the table, in a PDF version 5.0.5 format, 1,200 dpi. Filenames for each publication should include the number of the research project, the last name of the PI, the number of the publication and an abbreviated research project title. For example, if you submit two publications for PI Smith for the “Cognition and MRI in Older Adults” research project (Project 1), and two publications for PI Zhang for the “Lung Cancer” research project (Project 3), the filenames should be:

Project 1 – Smith – Publication 1 – Cognition and MRI

Project 1 – Smith – Publication 2 – Cognition and MRI

Project 3 – Zhang – Publication 1 – Lung Cancer

Project 3 – Zhang – Publication 2 – Lung Cancer

If the publication is not available electronically, provide 5 paper copies of the publication.

**Note:** The grant agreement requires that recipients acknowledge the Pennsylvania Department of Health funding in all publications. Please ensure that all publications listed acknowledge the Department of Health funding. If a publication does not acknowledge the funding from the Commonwealth, do not list the publication.

Title of Journal Article:	Authors:	Name of Peer-reviewed Publication:	Month and Year Submitted:	Publication Status (check appropriate box below):
1. None				<input type="checkbox"/> Submitted <input type="checkbox"/> Accepted <input type="checkbox"/> Published

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

Yes   X   No \_\_\_\_\_

If yes, please describe your plans:

We are working on preparing the manuscript for submission to a peer reviewed journal.

**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.

## 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 <b>David Goldenberg, M.D.</b>	POSITION TITLE <b>Professor of Surgery and Medicine</b>		
eRA COMMONS USER NAME (credential, e.g., agency login) <b>DGOLDENBERG</b>			
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
Ben Gurion University of the Negev, Beersheva, Israel	B.Sc.	02/92	Medical Sciences
Ben Gurion University of the Negev, Beersheva, Israel	M.D.	02/95	Medicine
Soroka Medical Center, Beersheva, Israel		03/96	Internship
Rambam Medical Center, Haifa, Israel		03/02	Residency
Johns Hopkins Medical Institution and University School of Medicine, Baltimore, MD		06/05	Fellowship

### Personal Statement

I joined the faculty of the Division of Otolaryngology at The Pennsylvania State University College of Medicine, The Milton S. Hershey Medical Center in December, 2005, as an Associate Professor and Director of Head and Neck Oncology. My previous position was at The Johns Hopkins University School of Medicine in Baltimore, MD; first as a Fellow and then as an Attending Surgeon, Instructor of Otolaryngology-Head and Neck Surgery. Prior to that time, my post graduate medical training consisted of one year of internship at the Ben Gurion University School of Medicine in Beer Sheva, Israel, followed by six years of Otolaryngology - Head and Neck Surgery residency at the Technion, Israel Institute of Technology in Haifa, Israel. This was followed by a three-year fellowship in Head and Neck Oncology and Surgery combined with a one-year basic science postdoctoral fellowship at the Johns Hopkins University School of Medicine in Baltimore, MD.

### Positions and Honors

#### Positions and Employment

- 1995-1996 Internship, Soroka Medical Center-Ben Gurion University of the Negev Beer Sheva Israel
- 1996-2002 Residency Otolaryngology-Head and Neck Surgery Dept of Otolaryngology- Head and Neck Surgery- Rambam Medical Center, Haifa Israel
- 1999-2002 Instructor of Otolaryngology Bruce Rappaport Faculty of Medicine Technion, Israel Institute of Technology
- 2000-2002 Coordinator - Galil Center for Telemedicine and Medical Informatics Faculty of Medicine, Technion – Israel Institute of Technology
- 2002-2005 Fellow in Head and Neck Surgery- Dept of Otolaryngology- Head and Neck Surgery, Johns Hopkins University School of Medicine
- 2005-present Associate Professor of Surgery and Medicine- Pennsylvania State University, The M.S. Hershey Medical Center, College of Medicine, Hershey, PA
- 2011-present Professor of Surgery & Medicine-Pennsylvania State University, The M. S. Hershey Medical Center, College of Medicine, Hershey, PA

#### Honors and Other Professional Activities

- 2001 Outstanding Preclinical Lecturer Award - Head and Neck Anatomy, Bruce Rappaport Faculty of Medicine Award

2002 Post doctoral scholarship - Israel Cancer Society  
 2002 Post doctoral scholarship- Galil Center for Telemedicine and Medical Informatics, Bruce Rappaport Faculty of Medicine Award  
 2003 Basic Science Research Award- American Head and Neck Society  
 2004 Daiichi Clinical Scholar -Clinical Research and Biostatistics -American Academy of Otolaryngology- Head and Neck surgery  
 2005 Honor Award- American Academy of Otolaryngology- Head and Neck Surgery  
 2009 Alpha Omega Alpha Medical Honor Society

**Research Support**

**Ongoing Research Support**

Pennsylvania Department of Health Goldenberg /Robertson (Co-PI) 4/1/2009 – 6/30/2011  
 Commonwealth Tobacco Settlement (No Cost Extension)  
 Title: *P16* alteration and *BRAF* mutation and patient outcome in Papillary Thyroid cancer  
 Project goal: This project aims to link p16 alteration and BRAF mutation with poor outcomes.  
 Role: Co-PI

5 R03 DE000019511-02 Goldenberg/Hollenbeak (Co-PI) 9/8/2009 – 08/31/2011  
 NIH/ NIDCR  
 Title: Clinical and Financial Impact of Treatment for Oral and Pharyngeal Cancer  
 Project Goal: To assess the financial and clinical impact of different treatment approaches for oral and pharyngeal cancers.  
 Role: Co-PI

The Pennsylvania State University Goldenberg (PI) 7/1/2006 – 6/30/2011  
 College of Medicine, Department of Surgery- Surgery Feasibility Grant  
 Title: Opioid Growth factor in Differentiated and Undifferentiated Thyroid Cancer Cell Lines  
 Project goal: This project aims to link the opioid growth factor axis with thyroid cancer cell lines.  
 Role: PI

George L. Lavery Foundation Grant Goldenberg (Co-PI) 5/1/2010 – 4/20/2011  
 Title: Rising Rates of Thyroid Cancer in the Harrisburg Area (No Cost Extension)  
 Project goal: to ascertain not only if there is a difference in thyroid cancer rates in the Harrisburg area but whether these thyroid cancer cases were more aggressive, advanced or recurrent; and if so, why?  
 Role: Co-PI

The Pennsylvania State University Goldenberg (Co-PI) 7/1/2010 – 6/30/2011  
 College of Medicine, Department of Surgery – Dean’s Feasibility Grant  
 Title: Outcomes for Recurrent Thyroid Cancer in the Elderly  
 Project goal: To identify factors associated with variation in treatment for thyroid cancers in the Medicare population. To estimate the impact of different treatments on cost of medical care for patients with recurrent thyroid carcinomas, controlling for tumor features, demographic characteristics, and comorbid conditions.  
 Role: Co-PI

**Completed Research Support**

The Pennsylvania State University Goldenberg (PI) 7/1/2007 – 6/30/2008  
 College of Medicine, Department of Surgery-Surgery Feasibility Grant  
 Title: OGF-OGFr Axis and Inhibition of Human Thyroid Cancer: In Vivo Studies  
 Project goal: This project aims to link the opioid growth factor axis with thyroid cancer in nude mice.  
 Role: PI

## 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 Robertson, Gavin P.	POSITION TITLE  Professor		
eRA COMMONS USER NAME (credential, e.g., agency login) gprobertson			
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 (if applicable)	MM/YY	FIELD OF STUDY
California State University, Northridge, CA	B.A.	06/88	Molecular Biology
University of California, Riverside, CA	Ph.D.	03/97	Biomedical Sciences
Ludwig Institute for Cancer Research, San Diego, CA	Postdoc	03/97-03/00	Cancer Research

### Personal Statement

I am a tenured professor of Pharmacology, Pathology and Dermatology at the Penn State College of Medicine. I am also leader of our Melanoma Center and Director of the Penn State Melanoma Therapeutic Program. I have maintained consistent funding for my melanoma focused research program during my tenure at Penn State and currently have three funded NIH R01 grants. I started as an assistant professor and within 10 years became tenured and promoted to professor. I am an expert in the field of melanoma and my expertise ranges from gene discovery and validation to drug discovery and therapeutic development, which have resulted in more than 60 publications in these areas.

### Positions and Honors

#### Positions and Employment

1988	Student Assistant in Genetics, California State University, Northridge, CA
1989-1991	Coordinator of "Student Panels for an International Curriculum and Education" at Office of International and Exchange Programs, California State University, Northridge, CA
1987-1989	Drosophilla Stock Technician, California State University, Northridge, CA
1989-1991	Teaching Assistant in Cell Biology, California State University, Northridge, CA
1990-1991	Teaching Assistant in Embryology, California State University, Northridge, CA
1990-1992	Cytogenetic Technologist at Kaiser Permanente Regional Genetics Laboratory, CA
1992-1997	Research Assistant at University of California, Riverside, CA
1997-2000	Postdoctoral Fellow at the Ludwig Institute for Cancer Research, San Diego, CA
2000-2006	Assistant Professor (tenure track), Departments of Pharmacology, Pathology, and Dermatology, Penn State University College of Medicine, Hershey, PA
2006-2008	Co-Director, Drug Development and Discovery Core, Penn State University College of Medicine, Hershey, PA
2006-2010	Associate Professor (with tenure), Departments of Pharmacology, Pathology, and Dermatology, Penn State University College of Medicine, Hershey, PA
2008-2010	Associate Director for Translational Research, Penn State Cancer Institute, Penn State University, College of Medicine, Hershey, PA
2005-present	Director, Melanoma Therapeutics Program, Department of Pharmacology, Penn State University College of Medicine, Hershey, PA
2006-present	Director, Experimental Therapeutics Program, Penn State Cancer Institute, Penn State University College of Medicine, Hershey, PA
2010-present	Director, Melanoma Center, Department of Pharmacology, Penn State University College of Medicine, Hershey, PA

2010-present Professor, Departments of Pharmacology, Pathology, Dermatology and Surgery, Penn State University College of Medicine, Hershey, PA

### **Research Support**

#### **Ongoing Research Support**

No Number (Robertson) 01/01/04-12/31/15

Foreman Foundation

Melanoma Therapeutics Program Development

The goal of this project is to development of a Melanoma Therapeutics Program at Penn State.

5 R01 CA127892-05 (Robertson) 12/17/07-11/30/12

NIH/NCI

Akt3 Signaling as a Therapeutic Target

The goal of this project is to develop novel agents that inhibit Akt3 signaling in melanomas and synergize with agents inhibiting other signaling cascades.

5 R01 CA138634-02 (Robertson) 01/01/10-12/31/14

NIH/NCI

“Synergistically Acting Targeted Therapeutics for Melanoma”

Our long-term goal is to develop therapeutic agents that inhibit proteins deregulated in melanoma leading to synergistically acting tumor inhibition. Thus, the objective of this application is to develop the first-generation of these drugs by: (1) determining which kinases to target in melanoma cells in combination with Akt3 and V600EB-Raf to synergistically inhibit melanoma development; and (2) developing nanoliposomes containing siRNA targeting Akt3, V600EB-Raf and other key kinases to characterize utility for synergistically inhibiting metastatic melanoma development in animals leading to complete tumor regression.

5 R01 CA136667-02 (Robertson) 03/12/10-12/31/14

NIH

“Targeted Chemoprevention for Melanoma”

The objectives of this application are to first, evaluate the chemopreventive efficacy of novel nanoliposomes containing siRNA-targeting Akt3 and mutant V600EB-Raf, GSK3 $\alpha$  or Wee1 kinases in a transgenic animal model of the disease in which both Akt3 and V600EB-Raf are deregulated to promote spontaneous melanocytic lesion development. Second, we will determine whether these agents can prevent or decrease lymph node invasion by early melanocytic cells to decreased disease development and aid survival.

#### **Completed Research Support**

RSG-04-053-01-GMC (Robertson, Gavin P.) 1/1/2004-6/30/2009

American Cancer Society

Regulation of PTEN Signaling in Melanomas

The goals of this project are to provide unique information regarding the involvement of specific Akt isoforms in melanoma development and regulation of Akt isoform activity by PTEN.

5 R03 CA128033-02 (Robertson, Gavin P.) 9/1/2007-8/31/2010

NIH/NCI

Targeted Chemoprevention through Inhibition of Akt3 Signaling

The goal of this project is to characterize the chemopreventive potential of novel isothiocyanate derivatives that are effective for inhibiting Akt3 signaling.

Role: P.I.

## 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 <b>Saima Durvesh, M.D.</b>	POSITION TITLE <b>Assistant Professor of Medicine</b>		
eRA COMMONS USER NAME (credential, e.g., agency login) <b>sdurvesh</b>			
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>	YEAR(s)	FIELD OF STUDY
<b>Dow Medical College, Karachi, Pakistan</b>	<b>M.B., B.S</b>	<b>1993-1999</b>	<b>Medicine</b>

### A. Personal Statement

I joined the faculty of the Division of Endocrinology, Diabetes and Metabolism at The Pennsylvania State University College of Medicine, The Milton S. Hershey Medical Center in November, 2009, as an Assistant Professor. I completed my fellowship in Endocrinology, Diabetes and metabolism in August, 2009 at The Pennsylvania State University College of Medicine, The Milton S. Hershey Medical Center. Prior to that time, my post graduate medical training consisted of one year of internship at the A. Rehman Medical Center and Mideast medical Center in Karachi, Pakistan and three years of Internal medicine Residency at University of Texas Medical Branch (UTMB) Galveston, Texas.

I am a part time clinical attending physician. My current schedule is clinical activity with fellow, resident and student teaching, research and other administrative duties within the division.

### B. Positions and Honors.

#### Positions and Employment

2000 - 2001	Internship, Rehman Medical Center, Karachi, Pakistan
1999 - 2000	Internship, Mideast Medical Center, Karachi, Pakistan
2003 - 2006	Internship and Residency, Internal medicine, University of Texas Medical Branch, Galveston, Texas
2007 - 2009	Fellowship, Endocrinology, Penn state University College of medicine, the Milton S. Hershey Medical Center, Hershey, Pennsylvania
2009 - present	Assistant Professor of Medicine, Penn State University, Hershey, PA

#### Honors / Awards

2008 - 2009	Excellence in Research award – Department of Medicine, The Pennsylvania State University, College of Medicine, the Milton S. Hershey Medical Center, Hershey, PA
2005 – 2006	Winner of the Dr. Patsy Koeppe Award for Excellence as a PGY-2 Internal Medicine Resident, University of Texas Medical Branch, Galveston, Texas
1998 – 1999	Ranked 8 <sup>th</sup> in class in Final Professional MBBS Exam in Dow Medical College with honors in

- Internal Medicine and Pediatrics
- 1997 – 1998 Ranked 4<sup>th</sup> in class in 3<sup>rd</sup> Professional MBBS Exam in Dow Medical College with honors in Community Medicine
- 1996 – 1997 Ranked 2<sup>nd</sup> in class in 2<sup>nd</sup> Professional MBBS Exam in Dow Medical College with honors Pharmacology
- 1995 – 1996 Ranked 3<sup>rd</sup> in Karachi in 1<sup>st</sup> Professional MBBS Exam with honors in Anatomy, Biochemistry & Physiology & received scholarship by University of Karachi, Pakistan

**C. Selected Peer-reviewed Publications**

1. **Durvesh S**, Pichardo-Lowden A, Douglas S, Todd W, Bruno M, Goldenberg D. Anaplastic thyroid carcinoma in a young woman: a rare case of survival. *Thyroid*. 2009;19(7):775-779.

**D. Research Support**

**Ongoing Research Support**

None

**Completed Research Support**

Pennsylvania Department of Health	Goldenberg /Robertson (Co-PI)	4/1/2009 – 6/30/2011
Commonwealth Tobacco Settlement		(No Cost Extension)
Title: <i>P16</i> alteration and <i>BRAF</i> mutation and patient outcome in Papillary Thyroid cancer		
Project goal: This project aims to link p16 alteration and BRAF mutation with poor outcomes.		
Role: Co-Investigator		

## 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		
Manni, Andrea eRA COMMONS USER NAME amanni	Professor of Medicine		
EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)			
INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
University of Florence, Italy	M.D.	1970	Medicine

### A. Personal Statement

I lead a multi-disciplinary team of investigators at Penn State University as well as Fox Chase Cancer Center and Colorado State University testing more effective and safer chemopreventive strategies for breast cancer. Our research focuses on testing the merit of combining antiestrogens with omega-3 fatty acids with the goal of reducing the incidence of both estrogen receptor positive and estrogen receptor negative tumors. Our research consists of both preclinical studies in rodent models of mammary carcinogenesis as well as a randomized clinical trial in postmenopausal women at higher risk of breast cancer development based on high breast density. Numerous biomarkers of hormone metabolism, growth factor signaling, inflammation and oxidative stress are measured throughout our experiments to determine whether alterations in their level can be predictive of the antitumor action of our chemopreventive measures. This work is being supported by a five-year Komen Promise Grant (KG081632, \$5 million).

### B. Positions and Honors.

#### Professional Experience

1972 - 1973	Medical Internship, St. John Hospital, Detroit, MI
1973 - 1974	First-Year Medical Residency, Mt. Sinai Hospital, Cleveland, OH
1974 - 1975	Second-Year Medical Residency, Case Western Reserve University, Cleveland, OH
1975 - 1977	Endocrinology Fellowship, Case Western Reserve University, Cleveland, OH
1977 - 1978	Senior Instructor in Medicine, Case Western Reserve University, Cleveland, OH
1978 - 1981	Assistant Professor of Medicine, Case Western Reserve University, Cleveland, OH
1981 - 1984	Assistant Professor of Medicine, Penn State University, Hershey, PA
1984 - 1989	Associate Professor of Medicine, Penn State University, Hershey, PA
1989 - present	Professor of Medicine, Penn State University, Hershey, PA
2002 - present	Chief, Division of Endocrinology, Diabetes, and Metabolism, Penn State University

### C. Selected Peer-Reviewed Publications (from more than 170)

1. Hu X, Washington S, Verderame MF, Manni A. Interaction between polyamines and the mitogen-activated protein kinase pathway in the regulation of cell cycle variables in breast cancer cells. *Cancer Res.* 2005;65:11026-11033.
2. Manni A. Influence of polyamines on breast cancer biology. In: Wang JY, Casero RA, eds. *Polyamine Cell Signaling: Physiology, Pharmacology, and Cancer Research*. Humana Press: Totowa, NJ; 2006:139-153.
3. Manni A. Role of polyamines in breast cancer growth, development and progression. *Curr Cancer Ther.* 2005;1:207-215.
4. Jun JY, Griffith JW, Bruggeman R, Washington S, Demers LM, Verderame MF, Manni A. Effects of polyamine depletion by  $\alpha$ -difluoromethylornithine on *in vitro* and *in vivo* biological properties of 4T1 murine mammary cancer cells. *Breast Cancer Res Treat.* 2007;105(1):29-36.



**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 <b>Crist, Henry</b>		POSITION TITLE Assistant Professor	
eRA COMMONS USER NAME (credential, e.g., agency login)		Department of Pathology Penn State Hershey Medical Center & College of Medicine	
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
University of Maryland School of Medicine	MD	06/66	Medicine
Harrisburg Hospital	Internship	07/66 - 07/67	Medicine
US Public Health Service & Johns Hopkins Hospital	Residency	07/67 - 07/73	Pathology

**A. Personal Statement**

As Director of Surgical Pathology and practicing surgical pathologist, I have had extensive experience over several decades in the histopathology and diagnosis of cancer including expertise in head and neck tumors. My current research includes an epidemiologic evaluation of HPV subtypes and investigation of possible etiologies of aggressive squamous carcinoma; evaluation of the possible etiologic role of heavy metals in renal cell carcinoma; comparison of tumor markers to outcomes in patients with anaplastic thyroid carcinoma, and the evaluation of a potential indicator of aggressivity in papillary thyroid carcinoma. My experience in the field of oncologic surgical pathology provides the background for evaluation of BRAF mutation and P16 alterations in papillary thyroid carcinoma.

**B. Positions and Honor**

**Positions and Employment**

- 1973 - 1982 Associate Pathologist, Saint Joseph Hospital, Towson, Maryland (Exclusive of 4 Months July-October 1976)
- 1976 Associate Pathologist, Tucson Medical Center, Tucson Arizona (July-October)
- 1982 - 2005 Medical Director of Laboratories/Pathologist, Carlisle Regional Medical Center, Carlisle, Pennsylvania
- 1995 - 2001 Consulting Staff, Holy Spirit Hospital, Camp Hill, Pennsylvania
- 2005 - present Assistant Professor, Department of Pathology, Penn State College of Medicine and Penn State Milton S. Hershey Medical Center, Hershey, PA
- 2006 - present Director of Surgical Pathology, Department of Pathology, Penn State College of Medicine and Penn State Milton S. Hershey Medical Center, Hershey, PA
- 1973 - 1982 Instructor, School of Medical Technology, Towson State University, Towson, Maryland
- 1973 - 1976 Instructor (Teaching Appointment), Johns Hopkins University, School of Medicine, Department of Pathology & Division of Laboratory Medicine, Baltimore, Maryland

### **Other Experience and Professional Memberships**

1969 - present American Society of Clinical Pathologists  
1969 - present College of American Pathologists  
1970 - present United States and Canadian Academy of Pathology  
1971 - 2000 American Society of Cytopathology  
1973 - 1982 Maryland Society of Pathologists  
1982 - 1995 Pennsylvania Tri-County Society of Pathologists  
1982 - 2002 Central Pennsylvania Blood Banks Board of Directors  
1986 - 1989 Cerner Corporation  
1997 - 1998 Alliance 4 Health  
2007 - present Association of Directors of Anatomic and Surgical Pathology  
2010 - present International Society of Urologic Pathology  
2010 - present North American Society of Head & Neck Pathology

### **Honors**

2011 Dean's Award for Excellence in Teaching, Penn State College of Medicine

### **C. Peer-reviewed Publications**

1. Goldenberg D, Zagon IS, Fedok F, Crist HS, McLaughlin PJ. Expression of opioid growth factor (OGF)-OGF receptor (OGFr) axis in human nonmedullary thyroid cancer. *Thyroid*. Nov 2008;18(11):1165-1170.

### **D. Research Support**

#### **Ongoing Research Support**

None.

#### **Completed Research Support**

None.