AD_____

Award Number: DAMD17-99-1-9198

TITLE: Combined M.D./Ph.D. and Ph.D. Training Program in Breast Cancer Prevention

PRINCIPAL INVESTIGATOR: Robert B. Dickson, Ph.D.

CONTRACTING ORGANIZATION: Georgetown University Medical Center
Washington, DC 20057

REPORT DATE: July 2004

TYPE OF REPORT: Annual Summary

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

20050121 027

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	July 2004	Annual Summary (1 July 2003 - 30 Jun 2004)

4. TITLE AND SUBTITLE
Combined M.D./Ph.D. and Ph.D. Training Program in Breast Cancer Prevention

5. FUNDING NUMBERS
DAMD17-99-1-9198

6. AUTHOR(S)

Robert B. Dickson, Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Georgetown University Medical Center
Washington, DC 20057

E-Mail: dicksonr@georgetown.edu

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. Abstract ***(Maximum 200 Words)*** *(abstract should contain no proprietary or confidential information)*

The goal of this training program is to dramatically extend our existing, highly successful Interdisciplinary Doctoral Training Program in Tumor Biology with a new track which integrates genetics, molecular epidemiology, and prevention of breast cancer. This new track offers both MD/PhD and PhD training opportunities, and integrates new faculty from the Lombardi Comprehensive Cancer Center Programs in Cancer Prevention and Control, and Cancer Genetics. The program is enriched by new courses, as well as practical research experience. This new programmatic initiative make use of the existing organizational structure of the Interdisciplinary Doctoral training Program in Tumor Biology and incorporates a multi-disciplinary faculty who are devoted to research and education in breast cancer. To date, 10 students were recruited into 5 classes, and 4 new courses were created. Students in this program so far have published 9 papers, and 19 abstracts/presentations. They were also awarded 4 individual fellowship grants, and one has now been awarded her PhD, with others currently in the program continuing to make good progress toward that goal.

14. SUBJECT TERMS
breast cancer, interdisciplinary education, prevention, genetics, molecular epidemiology, translational research

15. NUMBER OF PAGES
10

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

COMBINED MD.PHD AND PHD TRAINING PROGRAM IN BREAST CANCER PREVENTION

Table of Contents

COMBINED M.D./Ph.D. TRAINING PROGRAM IN BREAST CANCER PREVENTION

INTRODUCTION

The goal of this program is to significantly extend our existing, highly successful Interdisciplinary Doctoral Training Program in Tumor Biology with a new track which integrates genetics, molecular epidemiology, and prevention of breast cancer. This new track offers both MD/PhD and PhD training opportunities, and integrates faculty from the Lombardi Comprehensive Cancer Center. To date, 5 MD/PhD and 5 PhD candidates were matriculated into this program. The program is enriched by new courses covering cancer genetics, molecular epidemiology, and cancer prevention, as well as practical research experience. To date, 4 new courses, including 2 electives and two core courses have been developed. This new programmatic initiative makes use of the existing organizational structure of the Interdisciplinary Doctoral Training Program in Tumor Biology and incorporates a multi-disciplinary faculty who are devoted to research and education in breast cancer. We have recently requested an extension of this grant period from 5 years to 6 years, in order to optimize our recruitment of the best qualified candidates for the available budget.

BODY

Training and Research Accomplishments

The accomplishments of this program, now finishing its fifth year, fall into two categories: the recruitment and progress of trainees, and the development of courses for the program. In the fifth year, we recruited Mr. Ogan Abaan and Ms. Maria Frech, Mr. Abaan received his BS and MS in Biology from the Middle East Technical University in Ankara, Turkey. Ms. Frech received her BS in Pharmacy from the Universidad Nacional de Rosar and has an MS in Food Technology from the Universidad Catolica Argentina; both Universities are in Rosario, Argentina. Mr Abaan will begin with a laboratory rotation with Dr. Toretsky, while Ms. Frech will initially rotate with Dr. Furth.

In the fourth year, we recruited Mrs. Youhoung Wang to the program. Mrs. Wang joined the Tumor Biology program with advanced standing, as she has transferred from University of Illinois' Microbiology and Immunology PhD program and has a MS degree in Cellular and Molecular Biology from Sun Yat-sen University of Medical Sciences in China. Mrs. Wang completed her laboratory rotations, passed her Comprehensive Exams and is now in PhD research with Dr. Dickson studying Cell Survival mechanisms. Ms. Wang received a DOD predoctoral Fellowship to support her work.

Ion Cotarla, M.D. appointed during the third year of the program, has completed his comprehensive examination and is working on the regulation and function of Stat5 in normal and malignant mammary epithelial cells, in Dr. Priscilla Furth's laboratory. Dr. Carlotta received a DOD Predoctoral Fellowship grant to support his work. Riddhish Shah, M.D., also in the third year of the program, is continuing his thesis research project, TGF beta regulator region polymorphism and its functional significance, with Dr. Carolyn Hurley. Rita Kralik, M.D., was also appointed into the third year of the grant, but elected to take an MS degree in Tumor Biology due to personal reasons.

Three trainees had been recruited for the second incoming class of the Program: one MD/PhD candidate, Ms. Carolyn Lee, and two PhD candidates, Ms. Sonia de Assis and Mr. Elijah Herbert. Ms. de Assis is in her fourth year of the program, she received a DOD predoctoral fellowship, and she is now working with her thesis mentor, Dr. Hilakivi-Clarke. Her thesis project concerns dietary factors during pregnancy and breast cancer. Ms. Lee completed her thesis research with Dr. Todd Waldman on breast cancer genetics and has just successfully defended her PhD thesis. She will re-enter Medical School this full to complete the MD portion of her training. Unfortunately, Mr. Elijah Herbert withdrew from the program after only a few months for very acute health reasons; we were able to use his slot in the program for recruitment of Ms. Carolyn Lee (above).

Two trainees had been recruited into the first incoming class, Ms. Christine Coticchia and Ms. Stacey Kessler. Ms. Coticchia has received a DOD predoctoral fellowship, and is proceeding with thesis research with Dr. Robert Dickson, studying c-Myc mediated apoptosis in mammary carcinoma cells. Unfortunately, Ms. Kessler withdrew from the program for personal reasons, but she earned an MS degree in Tumor Biology. However, the funds made available due to her departure were productively used to recruit a student with advanced standing into the third class (Sonia deAssis, see above).

In addition to the existing core course work of our GU Interdisciplinary Doctoral Training Program in Tumor Biology, new course components have been incorporated into our Breast Cancer Prevention track since Spring, 2002. These include a course in Biostatistics, *Applied Biostatistics,* that has been refocused on statistical design and methodology for research rather than biostatistics theory, and a Cancer Genetics course, *Genetics, Health, and Society in the 21st Century*, which focuses on practical and ethical questions raised by genetic information and technology. Both courses have been very successful and continue to be offered. *Applied Biostatistics* has become a required course for Tumor Biology PhD and MS students. A new course in Genetics, *Human and Microbial Genetics*, had a successful first two years. Most recently, a *Cancer Prevention* and *Epidemiology* Course was created as a new core course.

All of these courses emphasize breast cancer, as most of the teaching faculty are extensively involved in breast cancer research. Interest in these courses has not been limited to students in the new Breast Cancer Prevention track: a number of additional students in the Interdisciplinary Doctoral Training Program in Tumor Biology and other biomedical graduate programs at Georgetown University have enrolled as well.

KEY ACCOMPLISHMENTS

- *Recruitment of New Trainees and Advancement of Existing Trainees:*

Class #5
- Ms. Maria Silvina Frech began with a laboratory rotation with Dr. Priscilla Furth, and then worked with Dr. Suzette Mueller.
- Mr. Ogan Abaan has begun with a laboratory rotation with Dr. Toretsky.

Class #4
- Mrs. Youhong Wang has begun her PhD thesis work with Dr. Dickson.

Class #3
- Riddhish Shah, M.D. continues in his thesis research with Dr. Hurley.
- Ion Cotarla, M.D. continues his thesis research portion of the program. with Dr. Hurley

Class # 2
- Ms. Carolyn Lee completed her thesis research with Dr. Waldman, successfully defended her thesis, and will re-enter GU Medical School this full to complete her MD/PhD training.
- Ms. Sonia de Assis continues her thesis research with Dr. Hilakiv-Clarke.

Class # 1
- Ms. Christine Coticchia is in the final year of her thesis research with Dr. Dickson. She is expected to defend her thesis early in 2005.

REPORTABLE OUTCOMES

- *Student Publications:*

- Deb TB, **Coticchia CM**, and Dickson RB, Calmodulin-mediated activation of Akt regulates survival of c-Myc over-expressing mouse mammary carcinoma cells. J. Biol. Chem., in press, 2004.

- Ramljak D, **Coticchia CM**, Nishanian TG, Saji M, Ringel MD, Conzen SD, and Dickson RB. Epidermal Growth Factor Inhibition of c-Myc-mediated Apoptosis Through Akt and Erk involves Bcl-xL upregulation in mammary epithelial cells, Experimental Cell Research, 287:397-410, 2003

- Cavalli LR, Urban CA, Dai D, **De Assis S**, Tavares DC, Rone JD, Bleggi- Torres LF, Lima RS, Cavalli IJ, Issa J-PJ, and Haddad BR. Genetic and Epigenetic

Alterations in Sentinel Lymph Nodes Metastatic Lesions Compared to Their Corresponding Primary Breast Tumors. Cancer Genet Cytogenet 145:1-8, 2003.

- Waldman T, **Lee C**, Nishanian TG, and Kin JS. Human Somatic Cells Gene Targeting. In: Current Protocols in Molecular Biol. John Wiley & Sons. (In Press), 2003.

- Hruska KS, Tilli MT, Ren S, **Cotarla I**, Kwong T, Li M, Fondell JD, Hewitt JA, Koos RD, Furth PA, and Flaws JA. Conditional Over-Expression of Estrogen Receptor Alpha in a Transgenic Mouse Model. Transgenic Research 11: 361-372 2002.

- **de Assis S**, Ambrosone CB, Wustrack S, Krishnan S, Freudenheim JL, and Shields PG. Microsomal Epoxide Hydrolase Variants Are Not Associated with Risk of Breast Cancer. Cancer Epidemiology, Biomarkers, and Prevention 11(12): 1697-1698 2002.

- Hilakivi-Clarke L, Cho E, Cabanes A, **de Assis S**, Olivo S, Helferich W, Lippman ME, and Clarke R. Dietary Modulation of Pregnancy Estrogen Levels and Breast Cancer Risk Among Female Rat Offspring. Clin Cancer Res 8: 3601-3610. 2002.

- Hilakivi-Clarke LA, Cho E, **de Assis S**, Olivo S, Ealley E, Bouker KB, Welch JN, Khan G, Clarke R, and Cabanes A. Maternal and prepubertal diet, mammary development and breast cancer risk.. J Nutr, 131:154-157, 2001.

- Harris VK, Kagan BL, Ray R, **Coticchia CM**, Liaudet-Cooperman ED, Wellstein A, Riegel AT. Serum induction of the fibroblast growth factor-binding protein (FGF-BP) is mediated through ERK and p38 MAP kinase activation and C/EBP-regulated transcription. Oncogene Mar 29;20(14):1730-1738, 2001.

- *Student Abstracts/Presentations:*

  - **Frech MS**, Halana Ed, Jilli MT, Chodosh LA, Flaus JA, and Furth PA, Dysregulating expression of estrogen receptor in a mammary epithelial cells results in development abnormalities and ductal hyperplasia. *American Society for Investigative Pathology Meeting*, Washington, DC, 2004

  - **Shah R,** Hurley C, and Posch P, Differential binding of nuclear factors to the common TGF β1 promoter region single nucleotide polymorphisms-509 C to T and -800 G to A and their potential significance, *2004 Experimental Biology (Annual FASEB meeting),* AAI division, Washington DC. *Oral and poster presentations* (Block Symposium: Cytokine regulation, polymorphisms and chromatin).

- **Shah R,** Hurley C, and Posch P, Identification and characterization of transforming growth factor β1 promoter alleles, *2004 6th Annual Lombardi Science Research Fair – Student Division* – First Prize.

- **Shah R,** Polymorphisms in the extended 5' region and signal sequence of human TGF β1 and its functional importance, *2004 GUMC Student Research Fair.*

- **Shah R,** Characterization of differential nuclear factor binding to common SNPs in transforming growth factor β1 and its functional significance, *2004 GUMC Graduate Student Research Fair.*

- **Abaan OD**, Levenson A, Uren A, and Toretsky JA, The protein tyrosine phosphatase PTPL1 modulates ewing's sarcoma tumorigenesis. *95th Annual American Association for Cancer Research (AACR) Meeting,* Orlando, Fl, 2004.

- **Abaan OD**, Levenson A, Khan O, Furth PA, Uren A, Toretsky JA, The protein tyrosine phosphatase PTPL1 is a direct transcriptional target of EWS/FLI1 and modulates ewing's sarcoma tumorigenesis. *Lombardi Research Fair,* Washington, DC 2004.

- **de Assis S**, Cabanes A, and Hilakivi-Clarke L. Alcohol intake during pregnancy reverses the pregnancy-induced increase in p53 expression in the rat mammary gland. *American Association for Cancer Research,* Washington, DC 2003.

- **Cotarla I**, and Furth PA. Critical interactions between activated Stat5a and PI3K/Akt signaling pathways in normal and malignant mammary epithelial cells. *American Association of Cancer Research,* Washington, DC 2003.

- **Cotarla I**, Ren S, Li M, Zhang Y, Ghehan E, Singh B and Furth PA. Stat5 is activated in human breast cancers and associates with the p85 subunit of PI-3 kinase. Poster. Georgetown University Department of Medicine Research Day, Washington, DC; April 4, 2002. *Graduate Student Organization Research Day*; April 16-17, 2002. Meeting Abstract. *Proc Soc Exp Biol Med*, Washington D.C. Chapter Graduate Student Research Forum, Washington, D.C.; April 2002.

- **Cotarla I**, Ren S, Li M, Khan GA, Hilakivi-Clarke LA and Furth PA. Regulation and function of activated Stat5 in normal and malignant mammary epithelial cells. Poster 4th Annual Lombardi Research Fair, Washington, DC; February 19, 2002; *Georgetown University 16th Annual Student Research Day*, Washington, DC; February 21, 2002.

- **de Assis, S**, Ambrosone, CB, Wustrack, S, Krishnan, S, Frudenheim, JL, Shields, PG. Microsomal epoxide hydrolase polymorphisms and tobacco smoking in relation to risk of breast cancer. *American Association for Cancer Research*, San Francisco, CA, 2002.

- **de Assis S**, Ambrosone CB, Wustrack S, Krishnan S, Freudenheim JL, Shields PG. Microsomal Epoxide Hydrolase Polymorphisms and Tobacco Smoking in Relation to Risk of Breast Cancer. *DOD ERA of Hope Meeting*, Orlando, FL, 2002.

- **de Assis S,** and Shields PG. Microsomal Epoxide Hydrolase Polymorphisms and Tobacco Smoking in Relation to Risk of Breast Cancer. *4th Annual Lombardi Research Fair*. Georgetown University Medical Center, Washington, D.C. 2002.

- **Coticchia CM**, and Dickson RB. The role of c-Myc overexpression in sensitization of mammary epithelial cells to apoptosis. *DOD ERA of Hope Meeting*, Orlando, FL, 2002.

- Ramljak D, **Coticchia CM**, Nishanian TG, and Dickson RB. AKT inhibits c-Myc-mediated apoptosis in mammary epithelial cells: a mechanistic investigation. *DOD ERA of Hope Meeting*, Orlando, FL, 2002.

- **Coticchia CM**, Wang J-K, Dickson RB. Evaluation of pathways involved in C-Myc-induced apoptosis of mouse mammary carcinoma cells. *4th Annual Lombardi Research Fair*. Georgetown University Medical Center, Washington, D.C. 2002.

- **Lee C,** Waldman T. Functional Analysis of PTEN in Human Cancer Cells by Human Somatic Cell Gene Targeting. *4th Annual Lombardi Research Fair*. Georgetown University Medical Center, Washington, D.C. 2002

- Selaru FM, Xu Y, Yin J, Shustova V, Zou T, Twigg C, Abraham JM, Mori Y, Sato F, **Cotarla I,** Greenwald BD and Meltzer SJ. Microarray and bioinformatics analyses discriminate among biologic subtypes of esophageal neoplasia. Meeting Abstract. *Gastroenterology*, 120 (5): 226, Suppl. 1, April 2001.

- *Postdoctoral Fellowship Awards:*

  - **Christine Coticchia** received a DOD Fellowship Award in 2001 - Fas/Fas L System on c-Myc Expressing Mammary Carcinoma Cells.

  - **Ion Cotarla** received a DOD Fellowship Award in 2003 - Nucleocytoplasmic Export of Stat5 in Normal and Malignant Mammary Epithelial Cells: Regulation and Implications in Breast Cancer.

  - **Sonia de Assis** received a DOD Fellowship Award in 2003 – Pregnancy Leptin Levels and Breast Cancer Risk.

  - **Youhong Wang** received a DOD Fellowship Award in 2004 – Transcription factor stat5 in invasion and metastasis of human breast cancer.

- *Thesis Defense:*

  - **Carolyn Lee** successfully defended in 2004 her PhD thesis entitled: "Genetic Analysis of PTEN Function in Human Cancer Cells"

The goal of this training program is to dramatically extend our existing, highly successful Interdisciplinary Doctoral Training Program in Tumor Biology with a new track which integrates genetics, molecular epidemiology, and prevention of breast cancer. Additionally, new course components have been incorporated into the Breast Cancer Prevention track that focus on cancer genetics, cancer prevention, and epidemiology and cancer risk.