AD_____

GRANT NUMBER DAMD17-94-J-4421

TITLE: Breast Cancer Research Training Grant

PRINCIPAL INVESTIGATOR: Adrianne E. Rogers, M.D.

CONTRACTING ORGANIZATION: Boston University School of Medicine
Boston, Massachusetts 02118

REPORT DATE: October 1997

TYPE OF REPORT: Annual

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

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6. AUTHOR(S)
Adrianne E. Rogers, M.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Boston University School of Medicine
Boston, Massachusetts 02118

8. PERFORMING ORGANIZATION REPORT NUMBER

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13. ABSTRACT *(Maximum 200*

The purpose of the program is to train predoctoral students at Boston University Schools of Medicine and Public Health (BUSM, BUSPH) in research into the etiology, prevention, detection, diagnosis and therapy of breast cancer using the most advanced knowledge and techniques available. In addition to providing training in the student's chosen discipline, the program ensures her or his education in other relevant disciplines. Emphasis is placed on interdisciplinary training in Pathology, Epidemiology, and Cell and Molecular Biology. The goal is that, upon completion of the degree in a particular discipline, trainees will be able to work and communicate effectively with other scientists in interdisciplinary approaches to breast cancer research. This is being accomplished through an interdepartmental curriculum, selection of research supervisors whose research is in breast cancer or highly relevant to breast cancer and participation in working groups and seminars. Eight trainees, two per year, have been selected on the basis of their GPA, GRE scores, letters of recommendation, interviews, and demonstrated ability in and commitment to research, particularly in breast cancer. All trainees complete a practical course in mammary carcinogenesis studies in rats or mice. Six have completed their first-year or first-two-year courses and are completing laboratory rotations or beginning dissertation research; three have passed the qualifying examination. The two just admitted are beginning course work. In addition to support from this grant, trainees are supported by tuition and stipend given by BUSM and BUSPH.

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Training Program, Breast Cancer, Research Breast cancer research training Trainees	61
	16. PRICE CODE

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FOREWORD

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NA In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Resources, National Research Council (NIH Publication No. 86-23, Revised 1985).

NA For the protection of human subjects, the investigator(s) adhered to policies of applicable Federal Law 45 CFR 46.

NA In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.

NA In the conduct of research utilizing recombinant DNA, the investigator(s) adhered to the NIH Guidelines for Research Involving Recombinant DNA Molecules.

NA In the conduct of research involving hazardous organisms, the investigator(s) adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories.

Richard E. Rogers MD 10/21/97

PI - Signature / Date

4. Table of Contents

BREAST CANCER RESEARCH TRAINING PROGRAM (BCRTP)

5. INTRODUCTION

Information about breast cancer is increasing rapidly from many sources, but much of it is inconsistent and controversial because of the complexity of the disease and its causes. Difficulties arise also in integration of knowledge and understanding and in extrapolating results between and within scientific disciplines The Program in Research on Women's Health at Boston University Medical Center (BUMC) has been developed to address some of these problems by serving as an integrating and promoting force for research in women's diseases with a major effort focused in breast cancer research. Through the research and teaching collaborative efforts already in place and with the stimulus of this Training Program the work of investigators at BUMC is being brought to bear on training students to conduct research on breast cancer.

The **PURPOSE** of the Program is to: 1) establish a formal multidisciplinary research and academic training program in breast cancer biology and epidemiology; 2) produce graduates in one discipline (Pathology, Epidemiology, Microbiology) who have an understanding of the other disciplines and who can perform collaborative, multidisciplinary research in the etiology, prevention and therapy of the disease; 3) provide training in cell and molecular biology, experimental pathology, carcinogenesis, epidemiology and biostatistics, immunology, toxicology, and nutrition that will permit trainees to explore: a) basic breast cancer cell processes and interactions, including oncogene regulation, cell signalling, and genetic considerations in design of therapeutic agents; b) questions about etiology, prevention and therapy of breast cancer in laboratory animals and human populations; and c) the integration of knowledge derived from the different approaches; 4) maintain and increase collaborative research in breast cancer and closely related areas among faculty and trainees; 5) provide attractive opportunities for all students and, specifically, for women and underrepresented minorities to pursue careers in breast cancer research. We are promoting the development of young investigators who will have a broad, multidisciplinary background in breast cancer biology and epidemiology and intensive training in a specialized research area and who can perform significant research using advanced concepts and techniques and communicate research accomplishments effectively. They will be a resource to meet future personnel requirements for breast cancer research.
The **METHODS** are as follows. Doctoral students committed to cancer research with an interest in breast cancer research are admitted to the Departments of Pathology

and Laboratory Medicine or Biostatistics and Epidemiology and follow a curriculum specifically designed for this Training Program. BCRTP ensures that each predoctoral student: 1) participates in an appropriate, integrated curriculum focused on breast cancer; 2) has an advisory committee, composed of basic science and epidemiology faculty members with expertise in or closely related to breast cancer research; 3) participates actively in seminars, and local, regional and national meetings in addition to informal research meetings at the school.

The students are closely integrated into the Breast Cancer Working Group in the Program in Research on Women's Health. The Group comprises over 50 members in multidisciplinary teams collaborating in breast cancer research and developing new research strategies. The Group stimulates research interactions by providing teaching and discussion of clinical and research topics at monthly meetings. The BCRTP is significantly extending and supplementing the doctoral programs in the participating departments. The BCRTP is directed by Adrianne E. Rogers, MD, and Theodore Colton, DSc, with extensive input from Gail Sonenshein , PhD, and Marianne Prout, MD, who direct the Research on Women's Health Program.

Drs. Rogers and Colton meet with each other and with the Trainees and take responsibility for all decisions on student admission, performance and training with substantial input from the faculty Trainers and from the Trainees themselves. Because of the relatively small size of the Program and the extensive interactions with faculty in the Women's Health Program, the Admissions and Performance, Recruitment and Seminar Committees proposed have not been needed and, therefore, have not been formally set up.

The trainees are supported annually by the BCRTP and BUSM and BUSPH. The two schools have supplemented the BCRTG so that each student receives a stipend of $15,000-16,000 per year and tuition for 20-24 credits per year as needed. Drs. Rogers and Colton review the Program and its requirements and opportunities with the students and answer questions and plan each student's curriculum. Trainees are encouraged to consult any of the participating faculty for general advice or further discussion of their research interests, and are directed to appropriate faculty by Drs. Rogers and Colton. Trainees have additional contact with faculty members in courses and seminars.

Drs. Rogers and Colton have met also with each trainee at the end of each semester to discuss trainees' academic performance, to obtain feedback about the program and to advise the trainee on choice of courses and lab rotations. When the students move into their dissertation research, their Faculty Trainer will become their major adviser, but Drs. Rogers and Colton continue to meet individually with them at least once a year. After passing qualifying exams, trainees' research progress is reviewed on a regular basis by their dissertation committees, composed of three

members from the home department Training Faculty and one or more members each from the other two departments' Training Faculty. Under appropriate circumstances (need for a particular expertise), one of the committee positions may be filled by non-Trainer faculty from inside or outside BUMC. These committees meet with the trainee at least twice a year, usually starting within six months of the qualifying exam when the student presents her or his thesis research proposal. Finally, the thesis committee serves as the examining committee for the thesis defense.

6. **BODY**

The initial application was made to admit and support 4-7 trainees per year, but the grant awarded was for the partial support of 2-4 trainees per year.

The eight students are:

1994: Yvette Cozier (BA, Liberal Arts, Harvard Extension School, 1987; MPH, BUSPH, 1994) was admitted to the Biostatistics and Epidemiology DSc. program. She had extensive laboratory experience in Hematology and in Microbiology (1982-1994), strong letters from faculty and a 3.5 GPA at BUSPH. She was particulary interested in Dr. Lynn Rosenberg's epidemiological studies in breast cancer and other diseases in black women, and has joined Dr. Rosenberg's group for her dissertation research. She is currently supported by Dr. Rosenberg's research funds. Yvette is an African-American.

Laurie Hafer (BS, Microbiology, Penn. State Univ., 1989) was admitted to the Pathology and Laboratory Medicine Program. She had extensive clinical and research experience in the Immunohistochemistry laboratory at the College of Medicine-University Hospital, Hershey, PA, where she was in charge of research and development with a major focus on breast cancer studies. She had very strong letters from faculty who had supervised and worked with her. She entered intending to pursue interests in immunology and breast cancer but is now more interested in hormone receptor cellular and molecular biology and is performing her dissertation research in that area with Drs. Rogers and Traish. She has completed her course requirements and passed the qualifying examination in June, 1996. She is supported by Dr. Rogers' reseach funds and has submitted research grant applications to the DOD program and the Mass. Breast Cancer Research Program. She participated in the AACR Keystone workshop on Histopathobioogy of Neoplasia in July, 1996, and presented a poster there. She is one of ten students selected to give a platform presentation at the national DOD Breast Cancer Meeting, 10/31-11/3/97, in Washington, D.C. and has submitted an abstract to the national Society of Toxicology meeting in March, 1998.

1995. Sylvia Marecki (BS, Microbiology, Univ. N.H., 1995) was admitted by the Pathology and Laboratory Medicine PhD Program and is in the immunology track.

She had significant undergraduate research experience and was awarded two competitive research grants in addition to a four-year scholarship. She had very strong letters from her research adviser and other faculty. As we discussed research opportunities in Immunology, her interests shifted to cancer research from her initial focus on bacteriology, which was the subject of her undergraduate research. She has completed her course requirements and passed the qualifying exam in June, 1997. Sylvia is performing her dissertation research with Dr. Fenton in molecular biological studies of cellular (macrophage) immune responses. She is currently supported by Dr. Fenton's research funds.

Paul Johansen (formerly Mange) (BS Biology, Yale, 1988) was admitted to the Biostatistics and Epidemiology PhD program. This program differs from the DSc program in the SPH in being a more extensive joint program with the Mathematics Dept. on the Charles River Campus of BU and in requiring a more sophisticated mathematics and biostatistics curriculum and dissertation. After completing 1 1/2 years of medical school at Univ. Mass, Paul left to pursue interests in math and statistics and worked in biomedical applications of these areas as Sr. Research Analyst in Psychiatric Epidemiology at the Mass. General Hospital. He had excellent letters from faculty and colleagues. Paul completed his courses, passed his qualifying examination and is beginning his dissertation research with Dr. Timothy Rebbeck at the Univ. of Pennsylvania.

1996 Jackie Ashba (BA, Biology & Economics, Clark University, 1989; MPH, BUSPH, 1992; MA, BUSM, Medical Sciences, 1994) was admitted to the Epidemiology DSc program. Her Masters degree research included studies of both biological and epidemiological aspects of breast cancer. Her academic record here and her letters of recommendation are excellent. She is completing her courses and investigating several possibilities for dissertation research.

Ingrid Gherson (BS, Biology, Binghamton University SUNY) was admitted to the Dept. of Pathology and Laboratory Medicine. Her excellent undergraduate record (GPA 3.5) and GRE scores, strong letters of recommendation and significant technical experience in a pathology laboratory all are evidence of her potential for success in the program. She is completing her courses and has begun preparatory dissertation research on effects of vitamin D analogues on breast cancer cells with Dr. Ray.

1997 Kathryn Kavanagh(MD-PhD student at BUSM, admitted from the Royal College of Surgeons, Dublin, and following a year of molecular biology research at Albert Einstein College of Medicine). Kathryn has a 3.5 GPA here, is completing her course work and has begun working with Dr. Gail Sonenshein on studies of the inhibitor of NF-KB, IkB-α, in breast cancer.

Elizabeth Jiyoung Lee(BS, Microbiology and Genetics, UCLA). Elizabeth had excellent GRE scores and experience in studies in laboratory rodents; her research mentors wrote very strong letters. She is beginning course work and will start laboratory rotations in the spring.

The BCRTP students participate actively in the practical course in the setting up and running of DMBA mammary tumorigenesis studies under Dr. Rogers' direction. They learn basic methods for such studies, have participated in feeding, weighing and observing the animals and in performing necropsies for examination of tumors and collection of tissues for histological, endocrine and molecular studies. Members of the Pathology faculty introduce them to clinical studies of breast cancer. The subjects specifically covered are: Dr. De las Morenas: basics of breast cancer pathology; Dr. Burke: basics of image analysis, focused on estrogen receptor assay; Dr. Yang and one of the students, Laurie Hafer: basics of immunohistochemistry staining and interpretation; Dr. Rogers: basics of the histopathology of rat mammary gland tumors and discussion of recent research papers. All of the students except Ms. Lee have worked extensively in the DMBA project. She and Ms. Ashba will complete the other aspects of the practical course this year.

The students participated in both the Research in Women's Health and the Pathology seminar series and in Breast Cancer Working Group meetings in addition to a variety of other seminars in the two schools and in the Mass. Breast Cancer Research Program. This year the BCRTG hosted two special seminars (Appendix).

Research summaries from the Trainees are attached (Appendix)

7. CONCLUSIONS

The Program is actively recruiting, attracting and retaining excellent students from diverse backgrounds to focus on breast cancer research. The students are a cohesive group who study and work together well. There are productive discussions of data from the DMBA project within the group that foster the interdisciplinary goals of the program. They Trainees interact extensively with Drs. Rogers & Colton and with other students and faculty working in breast cancer research and working in clinical settings with breast cancer. They are doing well in course work and research. The interdisciplinary focus in strong, fostered by the practical course, the required epidemiology and pathology courses, seminars, and frequent formal and informal meetings of the students with Drs. Rogers and Colton. The students are progressing as expected (or more rapidly than expected) through their course work and into research, a commendable result.

8. References

None

9. APPENDIX

Meetings & Seminars

Breast cancer working group meetings and sub-group meeting:

12/10/96

4/29/97

4/30/97

5/13/97

5/27/97

5/28/97

6/10/97

6/24/97

8/12/97

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Boston University
School of Medicine

Program in
Research on
Women's Health

80 East Concord Street
Boston, Massachusetts 02118-2394
TEL: 617 638-4120
FAX: 617 638-5339

Gail E. Sonenshein, Ph.D.
Director
Marianne Prout, M.D., M.P.H.
Associate Director

Date: December 2, 1996

To: Breast Cancer Working Group

From: Drs. Marianne Prout and Gail Sonenshein

Re: Next group meeting

The next meeting of the Breast Cancer Working group is scheduled for:

Tuesday, December 10, 1996 from 4:00 to 5:00 pm in Room R108.

Please note new location and day! The meeting will focus on the carcinogen-driven rat model of mammary tumorigenesis. Dr. Adrianne Rogers will present an overview of the model. A group of investigators working with the model will then present their latest (hot) new data on expression of aromatic hydrocarbon and estrogen receptors, NF-κB, and c-*myc* oncogene. We will try to keep to schedule, i.e., end on time, so we may need an additional meeting to cover all of the new findings. We look forward to seeing you there.

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Program in Research on Women's Health

Interdisciplinary Seminar Series

Current Directions in Research on Women's Health

Co-Sponsored by:
The Massachusetts Department of Public Health
Breast Cancer Research Program

BREAST CANCER IN OLDER WOMEN

by

Rebecca Silliman, M.D., Ph.D.

Associate Professor of Medicine and Public Health
Boston University Medical School

Thursday
January 30, 1997
9:30-10:30 a.m.

Boston University School of Medicine
Evans Building, Room 112A

Refreshments will be served

BOSTON UNIVERSITY MEDICAL CENTER

Program in Research on Women's Health

Interdisciplinary Seminar Series

Current Directions in Research on Women's Health

in conjunction with
Department of Pathology and Laboratory Medicine

OBESITY, LEPTIN AND THE CONTROL OF FAT CELL METABOLISM

SHEILA COLLINS, PH.D.

ASSISTANT PROFESSOR
DEPT. OF PSYCHIATRY AND BEHAVIORAL SCIENCES
STEDMAN CENTER FOR NUTRITIONAL STUDIES
DUKE UNIVERSITY MEDICAL CENTER

WEDNESDAY, MARCH 19, 1997
1:00 - 2:30 P.M.
Room L-110

Boston University School of Medicine

Jointly Sponsored by

Department
of Pharmacology
and Experimental Therapeutics

Program in Research
on Women's Health

Female Reproductive Aging: A Window into the Aging Brain

Phyllis M. Wise, Ph.D.

Department of Physiology
University of Kentucky

Wednesday, 9 April 1997
2:00 PM
Refreshments at 1:45 PM

BOSTON UNIVERSITY MEDICAL CENTER

Program in Research on Women's Health

Interdisciplinary Seminar Series

Current Directions in Research on Women's Health

BREAST CANCER WORKING GROUP

Meeting Announcement

The next BCWG meeting will be presented by

DR. ABDUL TRAISH

Date: Wednesday, May 28, 1997
Time: 4:00-5:15 PM
Place: R-110

Refreshments will be served

BOSTON UNIVERSITY MEDICAL CENTER

Program in Research on Women's Health

Interdisciplinary Seminar Series
Current Directions in Research on Women's Health

Co-Sponsored by:
The Massachusetts Department of Public Health
Breast Cancer Research Program
and
Hematology/Oncology Section of B.U.S.M.

SIGNAL NETWORKS IN THE MAMMARY GLAND: LESSONS FROM ANIMAL MODELS

by

Lothar Hennighausen, Ph.D.
National Institute of Diabetes, Digestive and Kidney Diseases,
National Institutes of Health

Monday
June 2, 1997
4:00-5:00 p.m.
L-112

Refreshments served at 3:45 p.m.

(Student lunch with him)

Department of PATHOLOGY and Laboratory Medicine

Boston University School of Medicine, 80 East Concord Street, Boston, MA 02118-2394

PATHOLOGY SEMINARS, FALL TERM 1996
FRIDAYS, 1:15-2:30
ROOM L301, REFRESHMENTS AT 1:00

September

20 **Alexander Urbano**
Department of Pathology & Laboratory Medicine
Identification of novel endonucleases in drug-induced apoptosis of human leukemia.

27 **Jennifer Cermak**
Department of Pathology & Laboratory Medicine
The availability of dietary choline during pregnancy alters the brain development of offspring.

OCTOBER

11 **Dr. Joseph Loscalzo**
Cardiovascular Institue and Department of Medicine
Nitric oxide and homeostasis.

18 **Dr. Vasilis Zannis**
Departments of Medicine and Biochemistry
Apolipoprotein E and its role in the pathogenesis of cardiovascular disease and Alzheimer's disease.

20-22 Whitehead Institute Symposium at MIT **Cancer (Graduate Students encouraged to attend)**

25 NO SEMINAR

NOVEMBER

1 **Dr. David Seldin**
Department of Medicine & Microbiology
Oncogenes and anti-oncogenes to model lymphomagenesis in transgenic mice.

8 **Dr. James Hamilton**
Department of Biophysics
Detection of crystalline cholesterol and other lipids in atherosclerotic plaques by new NMR methods.

15 **Ken Matsui**
Department of Pathology & Laboratory Medicine
Proteasome regulation of Fas ligand.

22 **Dr. Ilana Gozes**
Department of Clinical Biochemistry
Sackler School of Medicine
Neuropeptide-related drug development against neurodegeneration.

29 HOLIDAY

DECEMBER

6 **Amy Williams**
Department of Pathology & Laboratory Medicine
Transcriptional regulation of platelet-derived growth factor.

13 **Dr. Gerhard Heinrich**
Department of Biomolecular Medicine
Zebrafish neurotrophins and trks.

PLEASE POST
Phone: 638-4500

Department of PATHOLOGY and Laboratory Medicine

Boston University School of Medicine, 80 East Concord Street, Boston, MA 02118-2394

PATHOLOGY SEMINARS, SPRING TERM 1997
FRIDAYS, 1:15-2:30
ROOM L301, REFRESHMENTS AT 1:00

FEBRUARY

14	**Alexander M. Trbovich** **Department of Pathology & Laboratory Medicine**	High and low molecular weight DNA cleavage in ovarian granulosa cells: Characterization and protease modulation in intact cells and in cell- free nuclear autodigestion assays.
21	**Dr. Walker McGraw** **Department of Medicine**	Proteases and inflammation.
28	**Nick Husni** **Department of Pathology & Laboratory Medicine**	TNF-α and the diabetic fibroblast: Implications for diabetes mellitus

MARCH

7	**Tracey Lodie** **Department of Pathology & Laboratory Medicine**	PU.1 regulation of HIV-LTR.
14	**VACATION - NO SEMINAR**	

WEDNESDAY - TIME CHANGE: 1:00-2:30, ROOM: L110

19	**Dr. Sheila Collins** **Department of Psychiatry and Behavioral Sciences** **Stedman Center for Nutritional Studies**	**Obesity, leptin and the control of fat cell metabolism.**
21	**Dr. Williams Wetsel** **Head, Hormone Action Workgroup** **Lab. of Cellular & Molecular Pharmacology** **NIEHS**	Regulation of luteinizing hormone-releasing hormone neuronal function.
28	**Dr. Marsha A. Moses** **Dept. Surgical Research** **Childrens Hospital**	Matrix metalloproteinases and their inhibitors:A role in angiogenesis and tumorigenesis.

continued on the back⇒⇒

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Boston University School of Medicine, 80 East Concord Street, Boston, MA 02118-2394

PATHOLOGY SEMINARS, SPRING TERM 1997
FRIDAYS, 1:15-2:30
ROOM L301, REFRESHMENTS AT 1:00

SPECIAL SEMINAR

MARCH 21, 1997

Dr. Williams Wetsel
Head, Hormone Action Workgroup
Lab. of Cellular & Molecular Pharmacology
NIEHS

Regulation of luteinizing hormone-releasing hormone neuronal function.

PLEASE POST
Phone: 638-4500

Department of [redacted] PATHOLOGY [redacted] and Laboratory Medicine

Boston University School of Medicine, 715 Albany Street, Boston, MA 02118-2394

PATHOLOGY SEMINARS, FALL TERM 1997
FRIDAYS, 1:15-2:30
ROOM L301, REFRESHMENTS AT 1:00

SEPTEMBER

26	Jacob Sloane Department of Pathology & Laboratory Medicine	Brain inflammation in pathologic aging.

OCTOBER

3	Dr. Sun Tam Mitotix, Inc.	The proteosome dependent proteolysis of a cell cycle inhibitory protein and its clinical relevance.
10	Dr. Gail Sonenshein Department of Biochemistry	NF-κB/Rel transcription factors promote tumor cell survival.
17	Jun Yao Department of Pathology & Laboratory Medicine	Soluble factors controlling tumor growth.
24	Dr. Peter Hudson Food and Drug Administration	Biotechnology and the FDA.
31	Anthony F. Trombino Department of Pathology & Laboratory Medicine	The aromatic hydrocarbon receptor/ transcription factor in the etiology of breast cancer.

NOVEMBER

7	Dr. Mary Ann Greco VA Medical Center West Roxbury/ Harvard Medical School	Choline acetyltransferase expression during sleep.
14	Laurie Hafer Department of Pathology & Laboratory Medicine	The effects of dietary fat and black tea on steroid hormone receptors in normal and neoplastic mammary glands in rats.
21	Eric Berg Department of Pathology & Laboratory Medicine	Heterogeneity of synaptic vesicles and possible implications in Alzheimer's disease.
28	**HOLIDAY**	

DECEMBER

5	Dr. Barbara Schreiber Department of Biochemistry	Cultured neonatal aortic smooth muscle cells: a model for function in atherosclerosis.
12	Dr. Adam Lerner Department of Medicine	cAMP Phosphodiesterases as a therapeutic target in human lymphoid malignancies.

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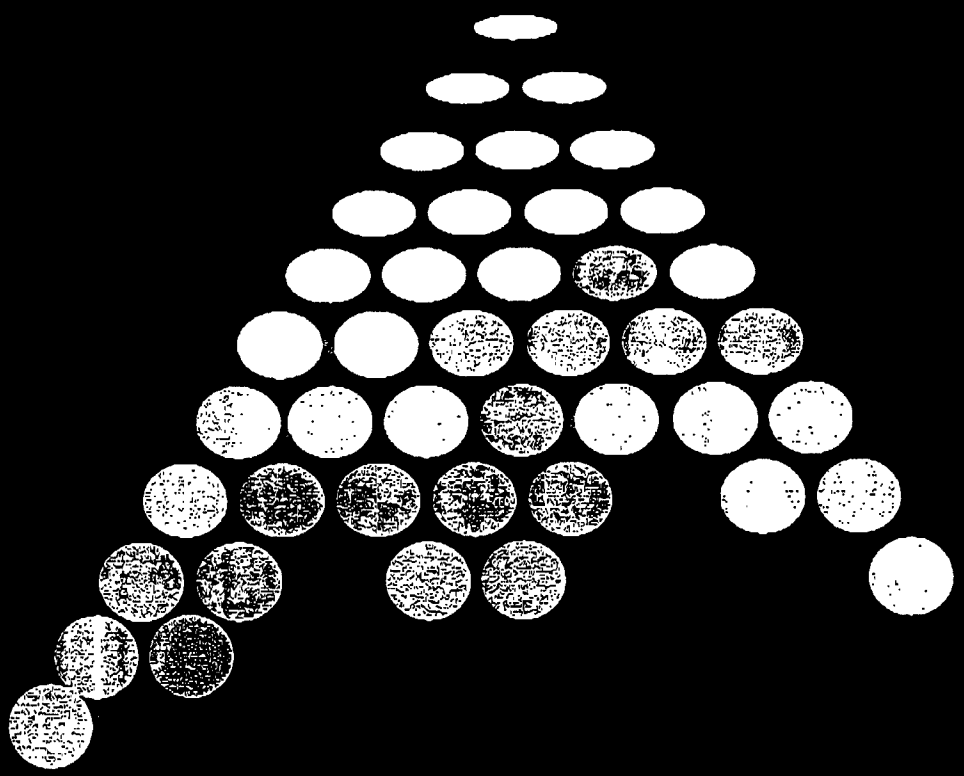
Women in Medicine and Science Series

1) December 3, 1996

2) April 16, 1997

CANCER

Whitehead Institute Symposium XIV
October 20 – 22, 1996



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CANCER

Sunday, October 20

Session I
8:00 pm –10:00 pm

Gerald R. Fink
Welcoming Remarks

KEYNOTE SPEAKERS

Richard Peto
"Big Numbers"

Robert A. Weinberg
"Seeking Master Switches in the Cancer Cell"

Monday, October 21

Session II
9:00 am –12:30 pm

ORIGINS

Chairperson: Albert de la Chapelle

Thomas Petes
"Genetic Control of Genome Stability in Yeast"

Yosef Shiloh
"Cellular Response to Damaged Macromolecules:
A Link Between Developmental Defects and Cancer"

Coffee Break

Alexander Kamb
"The Genetic Approach to Human Cancer"

Richard Klausner
"Cancer Genetics:
Dissecting a Tumor Suppressor Gene Pathway"

Lunch

Session III
2:00 pm –5:30 pm

MECHANISMS

Chairperson: Guillermina Lozano

David Beach
"Cell Cycle and Oncogene Cooperation"

Carol W. Greider
"Telomerase in Cellular Immortalization and Cancer"

Coffee Break

Charles J. Sherr
"G1 Phase Control and Cancer"

Eileen P. White
"Regulation of p53-dependent Apoptosis by the Bcl-2 Family"

Tuesday, October 22

Session IV
9:00 am –12:30 pm

PROGRESSION

Chairperson: Jerry Adams

Douglas Hanahan
"Apoptosis and Angiogenesis:
Biological and Genetic Parameters of Multi-Step Tumorigenesis"

Anton Berns
"Identification of Collaborating Oncogenes in Compound Knock-Out Mice"

Coffee Break

Allan Balmain
"The Genetic Basis of Tumor Predisposition and Tumor Progression in Mice"

Bert Vogelstein
"Colorectal Cancer"

Lunch

Session V
2:00 pm –5:30 pm

THERAPY AND DIAGNOSTICS

Chairperson: Judah Folkman

Allen Oliff
"Famesyl Transferase Inhibitors as Anti-Cancer Agents"

Frank McCormick
"A Strategy for Killing p53 Deficient Tumor Cells"

Coffee Break

David Sidransky
"The Emerging Molecular Microscope"

Thomas Waldmann
"The Promiscuous IL-2/IL-15 Receptor:
A Target for Radioimmunotherapy of Leukemia"

SPEAKERS

Jerry Adams
Walter and Eliza Hall Institute of Medical Research

Allan Balmain
CRC Beatson Laboratories

David Beach
Cold Spring Harbor Laboratory

Anton Berns
Netherlands Cancer Institute

Albert de la Chapelle
University of Helsinki

Judah Folkman
Harvard Medical School and Children's Hospital

Carol W. Greider
Cold Spring Harbor Laboratory

Douglas Hanahan
University of California, San Francisco

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Richard Klausner
National Cancer Institute

Guillermina Lozano
University of Texas M.D. Anderson Cancer Center

Frank McCormick
Onyx Pharmaceuticals

Allen Oliff
Merck Research Laboratories

Thomas Petes
University of North Carolina

Richard Peto
University of Oxford

Charles J. Sherr
St. Jude Children's Research Hospital and Howard Hughes Medical Institute

Yosef Shiloh
Tel Aviv University

David Sidransky
The Johns Hopkins School of Medicine

Bert Vogelstein
Johns Hopkins Hospital

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Eileen P. White
Rutgers University

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and participants may give out this number to receive messages.

LUNCH

Lunch will be served at 12:30 pm on Monday and Tuesday
in the MIT Student Center.
Luncheon tickets, which must have been purchased in advance,
must be presented for admission.

SYMPOSIUM ORGANIZERS

Gerald R. Fink, Chairman
Robert A. Weinberg
Eric Lander
Tyler Jacks
Edward Harlow
Peter M. Howley

Cancer Prevention and Control Grand Rounds

11/22/96

Cancer Prevention & Control Grand Rounds

Boston Medical Center

Evans Seminar Room / Evans Building / Noon - 1 p.m.

Please Post

Friday, February 21, 1997

"Physician-Assisted Suicide and the Terminally Ill Patient"

George Annas, JD, MPH, Edward R. Utley Professor and Chair,
Department of Health Law, Boston University School of Public Health

Friday, March 14, 1997

"Three Years After BRCA1: Genetic Testing for Breast Cancer Risk"

Judy Garber, MD
Director, Cancer Risk and Prevention Clinic, Dana-Farber Cancer Institute
Assistant Professor of Medicine, Dana-Farber Cancer Institute and Harvard Medical School

Friday, April 11, 1997

"How Should Physicians Discuss a Cancer Diagnosis? A Patient's View"

American Cancer Society (Massachusetts Division) volunteers:
Ms. Marilyn Morris and Mr. Lewis Brothers

Discussant/Moderator:
Dr. Phillip Freeman, Associate Director, Medical Student Program in Psychiatry

Friday, May 9, 1997

"How Can Physicians Help Their Patients to Stop Smoking?"

Judy Ockene, PhD, Professor of Medicine, Director, Division of Preventive and Behavioral Medicine, University of Massachusetts Medical Center

❖ **Lunch will be provided** ❖

1.2 hours Nursing CEUs / Physician CMEs

BOSTON MEDICAL CENTER

Boston University School of Medicine is accredited by the ACCME as a sponsor of continuing medical education for physicians. As an accredited institution, Boston University School of Medicine designates this continuing medical education activity for hour-for-hour credits in Category 1 towards the Physician's Recognition Award of the American Medical Association.

Boston University
School of Medicine

Department of
Pathology and
Laboratory Medicine
80 East Concord Street
Boston, Massachusetts
02118-2394
TEL: 617 638-4500
FAX: 617 638-4085

MEMORANDUM

TO: BCRTG Students

FROM: Adrianne E. Rogers, M.D.

DATE: March 3, 1997

SUBJECT: Special Seminar - Monday, March 10, 1997 - 4 P.M.

Dr. W.K. Hong will talk about retinoids and cancer prevention in the head and neck. The subject is highly relevant to breast cancer as well since vitamin A and synthetic retinoids prevent mammary gland carcinogenesis in rats. The epidemiological and statistical considerations are also, of course, highly relevant. Plan to attend if you can.

AER/cs

Special Seminar

11/7/96

Dr. Harold Varmus

CMF

Boston University School of Medicine
Department of Pharmacology and Experimental Therapeutics

STERLING DRUG VISITING PROFESSOR OF PHARMACOLOGY

BERT W. O'MALLEY, M.D.

Professor and Chairman
Department of Cell Biology
Baylor College of Medicine

Molecular Mechanisms of Steroid Receptor Action: 1997

Thursday, March 27, 1997
3:30 p.m.
Bakst Auditorium

Refreshments at 3:00 p.m.

Ligand - Independent Activation of Steroid Receptors

Friday, March 28, 1997
11:30 a.m.
L-112

Refreshments at 11:00 a.m.

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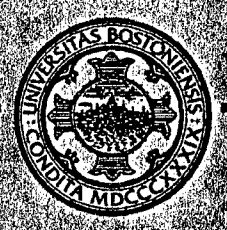
80 East Concord Street, Boston Massachusetts 02118



BOSTON UNIVERSITY SCHOOL OF MEDICINE
DIVISION OF GRADUATE MEDICAL SCIENCES

Presents

The Third Annual Henry J. Russek Student Achievement Day

"In the Middle of Difficulty Lies Discovery" A.E.

Rewarding Student Achievement
in the Disciplines of:
Anatomy and Neurobiology
Behavioral Neuroscience
Biochemistry
Biophysics
Microbiology
Pathology
Pharmacology
Physiology

April 18, 1997

Welcome to the Third Annual Henry J. Russek
Student Achievement Day

Today is a day of celebration. Due to the hard work of a unique group of students, faculty, and administrators, graduate education has become enriched by the necessity of providing a graduate research environment at BUSM that is integrated with the environment previously reserved for medical students. It is a pleasure to hear Deans and Chairpersons referring to their concerns over graduate student participation and the need to ensure that issues relating to both laboratory research and clinical practice be emphasized in the speeches at Commencement. However, these advances do not mean that all is done and we can now retreat into our laboratories never to emerge again. The environment that we enjoy today has been built by a select group of energetic students who left their mark in the original charter of the Graduate Student Organization. These students will soon leave to pursue their careers at institutions throughout the country and across the seas. Those of us that remain behind have a responsibility to keep the spirit alive by communicating to our new students the important value that we place on being an active participant in the process of graduate student education at the medical school. I am sure that Dr. Henry J. Russek, whose name accents our special day at the medical school, would indeed be proud to know that his day has contributed to igniting a new sense of purpose and initiative that burns in the halls and laboratories of the medical school campus. Thank you all again for your help in making this day a success. A special thank you to the following people: faculty members in each department who had to make the difficult decisions between excellent applicants; the dedicated members of the Division Award's Committee: Drs. Marlene Oscar-Berman, James Hamilton, David Larson, Alan Peters, Barbara Schreiber, Ray Stevens, and Herbert Kupchik; Sheila Welch for her help and enthusiasm; Susan Wilcox for her encouragement; Dr. Carl Franzblau for his commitment; Dean Chobanian for his recognition of the important role that basic science research plays in the medical school; Dr. David Farb for all his great ideas and dedication; Mrs. Elayne Russek for her generous support of graduate student education and research at BUSM; and all of our students who have devoted their time and energy to make today possible.

Have fun!

Best regards,

Shelley J. Russek

Shelley J. Russek, Ph.D.
Assistant Professor of Pharmacology
Chairperson Division Awards Committee

Program of Events:

Coffee and pastries available at 8:45 a.m.

9:00 -9:30 a.m.
Welcoming addresses by Jon Westling, President of Boston University, Dr. Aram Chobanian, Provost and Dean of Boston University Medical School, and Dr. Carl Franzblau, Associate Dean of the Division of Graduate Medical Sciences.

9:30-12:30 p.m.
Viewing of posters presented by graduate students enrolled in the Division of Graduate Medical Sciences (Buffet luncheon available at 11:30 a.m.)

12:30-2:30 p.m.
Slide presentations by the Henry J. Russek Student Achievement First Prize Recipients. Moderators: Mr. Garrick Lau, M.D./Ph.D. student in Pharmacology, and Mr. David Jackson, President of the Graduate Student Organization, Ph.D. student in Physiology. (Each presentation is 10 min. with an additional 5 min. for questions)

2:30-3:00 p.m.
Opening remarks by Dr. Carl Franzblau, Associate Dean of the Division of Graduate Medical Sciences, and award presentations by Mrs. Henry J. Russek, President of the Russek Foundation.

3:00 p.m. - 5:00 p.m.
Continued viewing of posters

Oral Presentations

12:30-12:40 p..m.
Frank Daly: Development and Degeneration of the Retina in a Mutant Zebrafish. (Department of Anatomy, Advisor: J. Sandell)

12:45-12:55 p.m.
Tracey Lodie: Both PU.1 and NF-κB Mediate LPS-Induced HIV-1 LTR Transcription. (Department of Pathology, Advisor: M. Fenton)

1:00-1:10 p.m.
Demetrios Vavvas: Dual Regulation of Acetyl-COA Carboxylase in Skeletal Muscle. (Department of Physiology, Advisor: N. Ruderman)

1:15-1:25 p.m.
Stephanie Kushner: Gamma-vinyl GABA Attenuates Both Cocaine-Induced Lowering of Brain Stimulation Reward Thresholds and Cocaine Self-Administration in Rats. (Department of Pharmacology, Advisor: C. Kornetsky)

1:30-1:40 p.m.
Nikos Makris: *In Vivo* Morphometry of Human Cerebral Association Pathways with Diffusion Weighted Imaging (DWI). (Program in Behavioral Neurosciences, Advisors: D. Pandya and D. Kennedy)

1:45-1:55 p.m.
Linda Foote: IL-4 Mediates Fas-Resistance in Anergic B Lymphocytes. (Department of Microbiology, Advisor: T. Rothstein)

2:00-2:10 p.m.
Kyriakos Kypreos: Basic Fibroblast Growth Factor Decreases Collagen Type V Levels, Through Induction of B-*myb* Expression. (Department of Biochemistry, Advisor: G. Sonenshein)

2:15-2:25 p.m.
Bin Lu: Structural and Functional Characterization of Human β2-Glycoprotein I. (Department of Biophysics, Advisor: M. Walsh)

Recipients of the Henry J. Russek Student Achievement Award '97

First Prize:

Frank Daly
Department of Anatomy and Neurobiology

Linda Foote
Department of Microbiology

Tracey Lodie
Department of Pathology

Bin Lu
Department of Biophysics

Nikolaos Makris
Program in Behavioral Neurosciences

Stephanie Kushner
Department of Pharmacology

Kyriakos Kypreos
Department of Biochemistry

Demetrios Vavvas
Department of Physiology

Second Prize:

Lei Jin
Department of Physiology

Martin Leach
Department of Pharmacology

Tom Schneider
Department of Microbiology

Ligaya Stice
Department of Biochemistry

Zaeem Siddiqui
Department of Anatomy and Neurobiology

Amy Williams
Department of Pathology

Chung-Kuo Wu
Program in Behavioral Neurosciences

Qing Yang
Department of Biophysics

Honorable Mention:

John Dumas
Department of Pharmacology

Stephanie Schauer
Department of Microbiology

Mika Sovak
Department of Pathology

Wei Sun
Department of Biochemistry

BOSTON UNIVERSITY SCHOOL OF MEDICINE AND THE DIVISION OF GRADUATE MEDICAL SCIENCES

PRESENT THE 1996 SERIES ON

the RESPONSIBLE CONDUCT *of* RESEARCH

Basic Rules and Policies

Research Involving Human Subjects

Leonard Glantz, J.D.

Professor of Public Health and Socio-Medical Sciences and Community Medicine, Co-Author of *Informed Consent to Human Experimentation: The Subject's Dilemma* and of *Children as Research Subjects: Science, Ethics & Law.*

The Boston University Policy on Scientific Misconduct

Michael Rosen, J.D.

Associate General Counsel, Boston University; Co-Author, *Boston University's Policies and Procedures Concerning Allegations of Misconduct in Scholarship and Research.*

The Scientific Use of Animals: A Changing Arena

Special Guest Speaker

Peter Theran, V.M.D.

Vice-President, Hospital Division and Director of Laboratory Animal Welfare,
Massachusetts Society for the Prevention of Cruelty to Animals/American Humane Education Society.
Member, National Research Council Committee for Long Term Care of Chimpanzees in Research.
Director of BUSM Laboratory Animal Science Center, 1966-1989.

(1)

Wednesday, September 18, 1996
3-5 pm in Room L-110

Attendance is required for pre- and post-doctoral trainees.

and please mark your calendars for..

(2)

Wednesday, October 23, 3-5pm in L-110
for a Presentation on Case Studies in Research Ethics

PRESENT THE 1997 SERIES ON

the RESPONSIBLE CONDUCT of RESEARCH

BOSTON UNIVERSITY SCHOOL OF MEDICINE AND THE DIVISION OF GRADUATE MEDICAL SCIENCES

PROBLEMS IN PROFESSIONAL ETHICS:
Avoiding Scientific Plagiarism

"I Couldn't Have Said It Better Myself"

Mary Williams, Ph.D.

Professor of Medicine and Anatomy and Neurobiology,
Co-Editor of *The American Journal of Respiratory Cell and Molecular Biology, 1988-1993*

"Original, With the Minimum of Alteration"

Christopher Ricks, M.A.

Professor of English, Boston University; Author of *T.S. Eliot and Prejudice* and *Beckett's Dying Words;*
Co-editor, *The State of the Language*

Panel Discussion Based on Case Studies

Joseph Loscalzo, M.D., Ph.D.
Professor and Chairman, Division of Medicine; Physician-in-Chief, Boston Medical Center,
Associate Editor, *The New England Journal of Medicine*

Christopher Ricks, M.A.

Johanna vanderSpek, Ph.D.
Assistant Research Professor of Medicine; Chair, Institutional Biosafety Committee

Susan Ward
Ph.D. Candidate, 1998, Behavioral Neurosciences Program

Mary Williams, Ph.D.
Moderator

Room L-110
3:30 - 4:45 pm
Thursday, February 27, 1997

Attendance is required for ıd *post-doctoral trainees.*

BOSTON UNIVERSITY SCHOOL OF MEDICINE AND THE DIVISION OF GRADUATE MEDICAL SCIENCES

PRESENT THE 1997 SERIES ON

the RESPONSIBLE CONDUCT *of* RESEARCH

IS THIS MY BODY, OR WHAT?

When and Under What Conditions May Human Tissue Be Used in Research?

The Context:

Norman G. Levinsky, M.D.

Professor of Medicine and Associate Provost, Boston University Medical Campus
Editor of *Xenotransplantation: Science, Ethics and Public Policy.*

The Realm:

Leonard Glantz, J.D.

Professor of Public Health and Socio-Medical Sciences and Community Medicine
Co-author of *Informed Consent to Human Experimentation: The Subject's Dilemma* and *Children as Research Subjects: Science, Ethics & Law*

The Rules:

John Bernardo, M.D.

Associate Professor of Medicine; Chairman, Boston Medical Center Institutional Review Board

The Case:

The facts of a lawsuit involving human tissue used in research will be distributed at the door.

Wednesday, October 15, 1997
3-4:30 pm
Room L-110

and please mark your calendars for...

Thursday, November 20 at 3 pm
for a session on laboratory animals presented by
the Institutional Animal Care and Use Committee (IACUC)

Attendance is required of all Pre- and Post- doctoral trainees and M.D.-Ph.D. and M.A. candidates.

Boston University
School of
Public Health
in the School of Medicine

Department of Epidemiology
and Biostatistics
80 East Concord Street
Boston, Massachusetts
02118-2394
617 638-5172

September 6, 1996

TO: Dr. Adrienne Rogers and Breast Cancer Trainees

FROM: Dr. Ted Colton TC

RE: Cancer Epidemiology Course

Attached is the schedule for this semester's course, EB 819: Cancer Epidemiology. Please note that a good number of the sessions concern breast cancer. Even if you are not registered for the course, you are welcome to attend any of the sessions that you feel would be of interest to you.

Boston University School of Public Health
Department of Epidemiology and Biostatistics
EB 819: Cancer Epidemiology Fall 1996
COURSE SCHEDULE
Thursday evenings, 6 to 8:45 pm Room L-301

Sep 5	Course outline and objectives	Colton & Zhang
	Biology of cancer	Prout
Sep 12	Cancer registration	Gershman
	Descriptive cancer epidemiology	Zhang
Sep 19	The SEER system of cancer registries	Colton
	Descriptive cancer epidemiology - continued	Colton
Sep 26	Cohort studies	Colton
	Bone mineral density and breast cancer	Zhang
Oct 3	Diethystilbestrol and cancer	Colton
	Seminar: Smoking and lung cancer	Zhang
Oct 10	Case-control studies	Zhang
	Magnetic field exposure and breast cancer	Coogan
Oct 17	Cancer clinical trials	Colton
	Breast Cancer Prevention Trial (tamoxifen)	Colton
Oct 24	Prostate cancer	Lesko
	Breast cancer	Rosenberg
Oct 31	Herbicide exposure and cancer	Clapp
	Skin cancer	Koh
Nov 7	Passive smoking and lung cancer	Siegel
	Female genital tract cancers	Shapiro
Nov 14	OPEN	
	OPEN	
Nov 21	Cancer and aging	Silliman
	OPEN	

Dec 5	Cancer screening	O'Brien
Dec 12	Cancer prevention Review and summary	Prout Colton & Zhang
Dec 19	FINAL EXAMINATION	

****

Course Instructors:

Theodore Colton, Sc.D.
Professor and Chair, Department of Epidemiology & Biostatistics
BUSPH Robinson 308 638-5172

Yuqing Zhang, Sc.D.
Assistant Professor of Medicine & Public Health
BUSM/BUSPH Robinson 611 638-8095

Guest Lecturers:

Richard Clapp, Sc.D.
Associate Professor of Environemntal Health
BUSPH Robinson 638-4620

Patricia Coogan, Sc.D.
Assistant Professor of Epidemiology & Biostatistics (pending)
BUSPH Robinson 638-5172

Susan Gershman, M.A.
Director, Massachusetts Cancer Registry
Massachusetts Department of Public Health 624-5646

Howard Koh, M.D., M.P.H.
Professor of Dermatology & Public Health
BUSM DOB 801A 638-7131

Sam Lesko, M.D.
Associate Professor of Epidemiology & Biostatistics
Slone Epidemiology Unit 734-6006

Michael O'Brien, M.D., M.P.H.
Professor of Pathology
BUSM Health Services Bldg 303D 638-6990

Marianne Prout, M.D.,M.P.H.
Associate Professor of Epidemiology & Biostatistics
BUSPH Vose 3 638-5038

Lynn Rosenberg, Sc.D.
Research Professor of Epidemiology & Biostatistics
Slone Epidemiology Unit 734-6006

Sidney Shapiro, M.B.
Research Professor of Epidemiology & Biostatistics and Director
Slone Epidemiology Unit 734-6006

Michael Siegel, M.D., M.P.H.
Assistant Professor of Behavioral Sciences
BUSPH

Rebecca Silliman, M.D., Ph.D.
Associate Professor of Gerontology and Public Health
BUSM DOB 1105 638-8387

Boston Area Graduate Student Symposium in Biology

Sponsored by: Harvard University School of Medicine

Saturday, April 19, 1997

Division of Medical Sciences
M.D.-P.H.D.
Series

1) April 23, 1997

2) September 22, 1997

Abstracts of Research in Progress from Training Grant Students

HORMONE RECEPTOR PHENOTYPES IN BREAST CANCER

Jacqueline Ashba, M.P.H. and Abdulmaged Traish, Ph.D.

ABSTRACT

Background: The effects of age on the expression of estrogen (ER) and progesterone receptors (PR) and prevalence of tumor phenotypes were examined in breast cancer patients. **Methods:** ER and PR concentrations were determined in tissue biopsies from 1740 specimens of patients with primary breast cancer, using ligand binding assays. Tumors were classified as receptor positive or negative for ER (ER+/-) and PR (PR+/-) based on the presence or absence of receptor binding activity. Tumors were stratified into four phenotypes based on ER and PR status: ER+ PR+, ER+ PR-, ER- PR+ and ER- PR-. **Results:** We observed a significant positive association between ER ($p=0.0001$), PR ($p=0.0003$) and age, but only the mean ER levels were statistically different between pre and postmenopausal patients. The prevalence of ER+PR+ tumor phenotype increased with age. In contrast, the prevalence of ER-PR- and ER- PR+ tumor phenotypes decreased with age. The PR to ER (PR/ER) ratio in ER+PR+ tumors decreased with age ($p=0.0001$) and this effect was mainly due to increased ER levels with age. **Conclusions:** These results indicate that ER concentrations may serve as a better predictor of response to endocrine therapy and disease-free survival in the management of breast cancer patients. The prevalence of ER-PR- and ER-PR+ tumors in younger patients suggest that hormonal regulation of ER gene expression may be responsible for the observed phenotypes.

Key words: Breast cancer, estrogen receptors, progesterone receptors, risk.

This work is supported by a grant from the Department of the Army DAMD 1794J4468

Yvette C. Cozier

The Black Women's Health Study (BWHS) is the largest ever study of the health of African-American women and is intended to assess risk factors for a variety of diseases. Similar studies, such as the Framingham Heart Study, and the Nurse's Health Study, have been ongoing for decades, and have resulted in much valuable health information. However, these studies have involved predominantly white populations. Considering that African-American women carry a greater burden of morbidity and mortality than white women for virtually every major illness [i] [iiiii]there is a growing recognition of the need for studies specific to black women.

The BWHS is a prospective cohort study funded by the National Cancer Institute (NCI). The cohort consists of 64,705 black women who completed questionnaires mailed in 1995 to subscribers to Essence Magazine, (read mostly by African-American women), their friends and family, as well as members of professional, community, and educational organizations. The questionnaires obtained extensive information on health, including the occurrence of breast cancer and potential risk factors for the cancer. Information was also obtained on health practices, including the use of mammography and breast self-examination. Subsequent biennial questionnaires will update information on exposures, illnesses, and lifestyle changes that have occurred since 1995. The first follow-up questionnaire was mailed in February 1997.

Analyses will be conducted to determine the extent to which the participants use mammography and practice breast self-examination, and to assess correlates of these health care practices.

(This work was supported in part by the US Army Medical Research and Material Command under DAMD17-94-J-4421)

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[i] Workshop Report, Epidemiology of Cancer in Minorities. Bethesda, MD: NCI, Division of Cancer Etiology, Epidemiology and Biostatistics Program, Extramural Programs Branch; 1990.

[ii] National Center for Health Statistics: Health, United States, 1989. Hyattsville, MD: Public Health Service; 1990.

[iii]Pickle LW, Mason TJ, Howard N, et al: Atlas of U.S. Cancer Mortality among Nonwhites, 1950-80. Washington, DC: US Government Printing Office, 1987. US Department of Health and Human Services, Public Health Service. NIH publication no. 90-1582.

ANTIPROLIFERATIVE EFFECTS OF COVALENTLY MODIFYING 1,25-DIHYDROXYVITAMIN D_3 ANALOGUES ON BREAST CANCER CELLS

Ingrid T. Gherson, Boston University School of Medicine, Department of Pathology and Laboratory Medicine, Boston, MA 02118

1,25-Dihydroxyvitamin D_3 ($1,25(OH)_2D_3$), the biologically active form of vitamin D, is a lipid-soluble seco-steroid functioning as a calcium and bone metabolism regulator. $1,25(OH)_2D_3$ has also been shown to mediate the proliferation and differentiation of several normal and malignant cell types. Since the discovery of a receptor for $1,25(OH)_2D_3$ in normal mammary gland as well as malignant breast tissues, investigators have studied the possibility of using $1,25(OH)_2D_3$ as a tumor growth inhibitor. Clinical use of $1,25(OH)_2D_3$ for cancer has been hampered due to the dose-limiting toxicity of hypercalcemia, hypercalciuria and soft tissue calcification. As a result, vitamin D analogues have been developed with strong anti-proliferative activity *in vivo* and *in vitro*, without inducing calcemic effects. This illustrates a potential role for $1,25(OH)_2D_3$ analogues in breast cancer therapeutics. We propose to study several bromoacetate derivatives of $1,25(OH)_2D_3$ for their ability to inhibit the *in vitro* proliferation of breast cancer cells. These $1,25(OH)_2D_3$ analogues differ from currently known anti-proliferative analogues in their ability to covalently modify the hormone-binding domain of the vitamin D receptor (VDR). Additionally, one such analogue has been shown to be more proliferative than $1,25(OH)_2D_3$ in cultured human keratinocytes. We shall examine antiproliferative/ prodifferentiative indices and assess apoptotic markers for each of the analogues in comparison to $1,25(OH)_2D_3$.

Key Words: 1,25-dihydroxyvitamin D_3, 1,25-dihydroxyvitamin D_3 analogues, apoptosis, antiproliferative effects.

Preliminary studies and proposal preparation performed under US Army Medical Research and Materiel Command under DAMD17-94-J-4221

BLACK TEA AND ESTROGEN AND PROGESTERONE RECEPTORS IN THE RAT MAMMARY GLAND

Laurie J. Hafer, Kristine E. Murphy, Adrianne E. Rogers, MD & Abdulmaged M. Traish, PhD

Boston University School of Medicine
& Mallory Institute of Pathology

Evidence of anticarcinogenic effects of dietary components has been reported. Extracts of green tea in particular have been shown to prevent or reduce carcinogenicity in the skin, lung, esophagus, forestomach and duodenum of laboratory rodents. Studies of black tea extracts have yielded similar results, but have been less extensive. Breast cancer, a leading cause of morbidity and mortality among women, has been shown to be modulated also by dietary intake in animal models, particularly intake of unsaturated fats, Vitamin A and selenium. Three studies of mammary gland carcinogenesis, in mice or rats, showed minimal or no evidence of a chemopreventive effect of tea. Bioassays in our laboratories have provided some evidence that tea reduced carcinogenesis in rats fed a high fat diet, but not in rats fed a control diet.

Since mammary glands and tumors are endocrine responsive and require estrogen for growth, we examined the levels of estrogen and progesterone receptors (ER, PR) in normal mammary glands and mammary gland tumors in the first bioassay by receptor-ligand binding assays. We have found suggestive evidence that PR levels were greater in normal mammary glands in rats given tea than in rats given water ($p=0.06$). Since PR synthesis is under estrogen control, we postulated that tea contains substances capable of binding the ER and may modulate its activity. Additional supporting evidence for this hypothesis was a suggestive, but not statistical, reduction in ER in tumors of tea-fed rats ($p=0.08$), indicating some tea components might be bound to the the cytosols of two ER(+) human breast cancers, two tea extracts, containing primarily catechins

Keywords: Estrogen Receptor, Progesterone Receptor, Steroid Hormone Receptors, Breast Cancer, Phytoestrogens

This work was supported by the U.S. Army Medical Research and Material Command under DAMD17-94-J-4421 and a grant from the Tea Trade Health Research Association.

or theaflavins, were shown to markedly inhibit [3H]-estradiol binding to ER. Similar results,using six different tea extracts and calf uterus as a source of ER, were shown. Preliminary in vitro experiments, using MCF-7 cells grown in RDGGS media at 37oC were performed. Cells were exposed to estradiol and tea extracts, lysed in buffer containing phosphatase inhibitors and analyzed by electrophoresis and immunoblotting, using our site-directed monoclonal antibody, EVG-F9. This antibody can distinguish between activated and non-activated forms of ER based on their electrophoretic mobility. A preliminary gel and blot showed that tea extracts do phosphorylate ER like estradiol does. These in vivo and vitro observations support the view that tea contains estrogen-like substances that can activate the ER. Therefore, these substances may influence mammary gland carcinogenesis, particularly in rats fed a high fat diet, via endocrine mechanisms.

Work is ongoing to determine whether ingestion of black tea extracts alters steroid hormone receptor concentration, distribution and activation in mammary glands or tumors, in rats fed control or high fat diets and studied at intervals from hours to months after DMBA administration; to correlate the results of biochemical and immunohistochemical receptor analyses to evaluate the hypothesis that tea and dietary fat influence mammary gland tumorigenesis via endocrine mechanisms; and to identify active tea extracts and compare their estrogenic and anti-estrogenic activities as defined by in vivo and in vitro biochemical, morphological and functional endpoints.

Title of Proposal: *Breast and Ovarian Cancer Risk Assessment Following Prophylactic Surgery: A Comparison of Statistical Models Using BRCA1 and BRCA2 Pedigree Data*

Principal Investigator: **Paul Mange Johansen**

Keywords: BRCA1/2, prophylactic surgery, Gibbs sampling, generalized estimating equations (GEE), frailty models

PROPOSAL ABSTRACT:

Women wishing to reduce their risk for breast and ovarian cancer have few means at their disposal. The primary risk factors for these diseases, gender, age, and family history, are not subject to individual control. Many women elect to undergo prophylactic mastectomy or prophylactic oophorectomy in the belief that the removal of much, if not all, normal tissue will decrease the likelihood of developing breast and/or ovarian cancer. Unfortunately, the extent to which these procedures reduce a woman's risk is unknown.

The identification of two genetic mutations, BRCA1 and BRCA2, has allowed women an opportunity to discover whether or not they are at elevated risk for developing the hereditary form of breast and/or ovarian cancer. Research on the benefits of prohpylactic surgery has utilized women with a heterogeneous set of risk profiles. This proposal will utilize data from the first study accounting for BRCA1 and BRCA2 status in evaluating the extent to which prophylactic surgery reduces a woman's risk of developing breast and/or ovarian cancer.

Between 250-300 women who have undergone bilateral prophylactic mastectomy or oophorectomy will be identified via 11 high-risk cancer registries across the United States and in the United Kingdom by the end of 1998. In addition, sisters of these surgical subjects without a history of prophylactic surgery will also be identified from these pedigrees.

A difficulty of interpreting such data is that statistical models often assume that information about one family member is independent of other family members. In many cases, however, this assumption is incorrect. A number of approaches to account for correlated data have been developed, including Gibbs sampling, generalized estimating equations (GEE), and frailty models.

This project will evaluate these three statistical techniques for incorporating potentially correlated data into models of risk assessment. Criteria will be established to measure the effectiveness of each model in estimating the reduction in cancer risk based on mutation status at BRCA1 and BRCA2. It is expected that the results from this proposal will be generalizable to other studies involving genetic risk factor assessment which employ pedigree data.

THE ROLE OF THE NF-kB INHIBITOR IkB-a IN THE PATHOGENESIS OF BREAST CANCER

Kathryn T. Kavanagh
Boston University School of Medicine
Department of Pathology and Laboratory Medicine

Keywords: breast cancer; NF-kappa B/Rel; I kappa B-alpha; environmental pollutants; antioxidants.

The incidence of breast cancer has been steadily rising over the past 50 years, and is now one of the leading causes of death among American women between the ages of 40-55. Recently, it has become apparent that bioaccumulation of environmental pollutants may be a contributing factor to this increase in disease incidence. The Polycyclic Aromatic Hydrocarbons (PAH's) such as 7,12-dimethylbenz(a)-anthracene (DMBA) are of particular interest. One of the earliest events in PAH tumorigenesis is the binding of the chemical to a cytosolic aromatic hydrocarbon receptor (AhR). The receptor-ligand complex is subsequently translocated to the nucleus where it can bind to and alter the transcriptional level of DNA that contains AhR-responsive elements. The Phase 1 cytochrome P450 family of enzymes is classically induced as a result of exposure to PAH's. These enzymes play a major role in the detoxification of harmful substances in the body, such as chemical carcinogens and drugs, by a process of oxidative metabolism. Often, reactive oxygen species (ROS) are produced during these metabolic reactions. ROS's are potentially harmful substances which are capable of causing DNA damage, and thus place the cell under considerable oxidative stress.

The Nuclear Factor-kappa B(NF-kB)/Rel family of transcription factors is an important link to the development of breast cancer. The family consists of p50, p65 (Rel A), c-Rel, Rel B and p52. NF-kB is a homo- or hetero-dimer, classical NF-kB being composed of p50 and p65. It was first identified as a protein family constitutively expressed specifically in mature B lymphocytes. In most non-B cells, inactive NF-kB protein is present sequestered in the cytoplasm complexed with inhibitory proteins called IkB's. Activation of NF-kB is achieved by phosphorylation of IkB which targets IkB for degradation via the proteosome-ubiquitination pathway. Free unbound NF-kB dimers translocate to the nucleus, where they can bind to kB responsive elements, causing upregulation of specific gene products. Activation and nuclear localization can be induced by several agents, including oxidative stress.

We hypothesized that the NF-kB/Rel family of transcription factors may be induced as a result of increased oxidative stress caused by environmental pollutants. This family of factors regulates transcription of multiple genes, including some involved in the regulation of cell proliferation and is known to be sensitive to the redox state of the cell. Our preliminary data support our hypotheses. We find that breast cancer cell lines and primary breast cancer tissue express significant levels of activated, nuclear NF-kB/Rel activity. The constitutive NF-kB expression, which regulates transcription of the c-myc oncogene, may promote aberrant proliferation and thus play an early role in the pathogenesis of breast tumors. The IkB family of inhibitors consists of several proteins, including IkB-a, IkB-b, p100 and p105 (p100 and p105 are also processed to form the NF-kB p52 and p50 subunits, respectively).

Antioxidants are thought to inhibit NF-kB/Rel activity. Green Tea is a substance known to contain several polyphenolic compounds which possess antioxidant properties. These compounds are the Green Tea Polyphenols (GTP), which include epicatechin, epicatechingallage epigallocatechin and epigallocatechin-3 Gallage (EGCG). Concentrated, purified polyphenol extracts of green tea have anticarcinogenic activity. Potential mechanisms of action include antioxidant activity, alteration of Phase I or Phase II enzymes in target or other tissues, anti-inflammatory activity and suppression

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of cell division. The toxicity of tea and of the polyphenols is low, and they are potentially important cancer chemopreventive agents for humans. We have been investigating the response of rodent mammary tumor models to green tea extract ingestion. Breast cancer, a major cancer in many populations, is susceptible to dietry modulation in several rodent models; variation in incidence in women is thought to be due, in part, to dietry patterns. We have quantitated 7,12-dimethylbenz(a)anthracene (DMBA)-induced mammary tumorigenesis in female Sprague-Dawley rats given extracts of green tea as the sole source of drinking water. DMBA is a chemical carcinogen which is found in the environment. The tea was given after a single, intragastric dose of DMBA. Rats were monitored by palpation for tumor development. Tumorigenesis was quantitated by latency (cumulative probability of bearing a tumor), tumor incidence, number and weight at necropsy.

Upon examination of these tumors at necropsy, it was found that rats who were administered green tea had a significantly lower tumor burden than rats who were not. Furthermore, after 14 weeks post-DMBA administration, the cumulative probability of bearing a palpable tumor was much higher in the control group of rats, compared with those fed green tea.

Initial Electrophoretic Mobility Shift Analysis (EMSA) of some of the rat breast tissue specimen indicate that tumors have markedly higher levels of NF-kB subunits than the histologically normal tissue samples. More detailed analysis of the samples are needed to determine which of the various subunits of NF-kB are expressed, in what quantities they are expressed, and the levels of IkBproteins that can be detected in these tissues.

CONTROL OF PRO-INFLAMMATORY GENE REGULATION; INTERACTIONS BETWEEN PU.1, NF-κB AND C/EBP

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In many inflammatory and pathologic states, such as atherosclerosis, tuberculosis, and cancer, macrophages are frequently recruited to the affected site. Specifically, macrophages are often detected by histology as infiltrating cells in solid tumors. Once recruited and activated, macrophages become key factor in the generation of an immune response. This can be mediated via the recruitment of other immune cells, or by the production of cytokines including interleukin-1 (IL-1), IL-6, and TNF. Activation of such inflammatory cascades in some instances is believed to induce tumoricidal activity in macrophages. The ability to regulate these immune and tumoricidal responses requires a better understanding of their molecular basis. Understanding the regulation of genes involved in these responses could provide a novel therapeutic approach in the treatment of many disease states, including breast cancer.

The focus of this study will be to gain an understanding of inducible macrophage gene expression at the level of gene transcription. Specifically, the potential interactions between the transcription factor PU.1 and two inducible transcription factors, NF-κB and C/EBP will be investigated. PU.1 is a myeloid- and B cell- specific member of the Ets family of transcription factors which binds to the DNA consensus sequence GGAA. Functional PU.1 binding sites are present in the promoters and enhancers of several pro-inflammatory genes. Work performed in this laboratory has demonstrated that although this transcription factor is constitutively present in the nucleus, it is not transcriptionally active until it is phosphorylated by Casein Kinase II. Stimulation of macrophages by lipopolysaccharide (LPS) leads to the phosphorylation and activation of PU.1. NF-κB and C/EBP are both inducible transcription factors that can be found in a wide range of cell types, including the macrophage. Like PU.1, these factors are also activated following LPS stimulation.

Previous work performed in this laboratory utilized the HIV-1 Long Terminal Repeats (HIV-LTR) as a model promoter/enhancer system to study inducible gene regulation. The HIV-LTR contains two tandem NF-κB sites that are located approximately 10 base pairs apart, a distance of one DNA helical turn. Our studies demonstrated that one of these NF-κB sites serves as functional PU.1 binding site. Additional work has shown that there may be a physical interaction between these two transcription factors when bound to the tandem NF-κB sites within the HIV-LTR. Thus, the HIV-LTR appears to be regulated by both NF-κB and PU.1

Furthermore, a C/EBP DNA-binding site also exists in close proximity to the two tandem NF-κB sites and others have postulated that this site is critical for transcriptional regulation. Work in progress includes further studies to define the interactions between these inducible transcription factors and their role in inducible gene expression. Future studies will identify the interaction domains within PU.1 that allow it to directly associate with other transcription factors. Specifically, immunoprecipitation studies will be undertaken using wild type and mutant PU.1 constructs including truncation mutants of PU.1 at both the N- and C-termini, deleting the trans-activation domain and C/EBPδ interaction domain, respectively. As these transcription factors (PU.1, C/EBP and NF-κB) are key players in the regulation of many pro-inflammatory genes, further analysis of their interactions will not only provide widely applicable insight into their regulation, but also provide novel targets for the design of new therapies to treat diseases such as

breast cancer.

KEY WORDS: Macrophages, inflammation, transcription factors

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