

AD _____

GRANT NO: DAMD17-94-J-4024

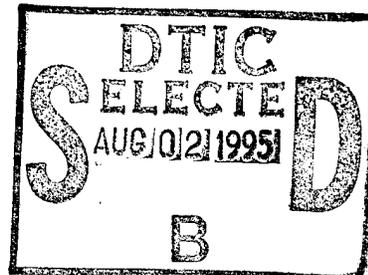
TITLE: Predoctoral Training Program in Breast Cancer Research

PRINCIPAL INVESTIGATOR: Lynn M. Matrisian, Ph.D.

CONTRACTING ORGANIZATION: Vanderbilt University Medical Center
Nashville, Tennessee 32732-2301

REPORT DATE: June 30, 1995

TYPE OF REPORT: Annual



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.

19950801 024

DTIC QUALITY INSPECTED 1

JLS

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

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 the 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 June 30, 1995	3. REPORT TYPE AND DATES COVERED Annual 6/1/94-5/31/95	
4. TITLE AND SUBTITLE Predoctoral Training Program in Breast Cancer Research		5. FUNDING NUMBERS DAMD17-94-J-4024	
6. AUTHOR(S) Lynn M. Matrisian, Ph.D.			
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Vanderbilt University Medical Center CCC-3322 Medical Center North Nashville, TN 32732-2301		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 None			
12a. DISTRIBUTION/AVAILABILITY STATEMENT Approved for public release; distribution unlimited		12b. DISTRIBUTION CODE	
13. ABSTRACT (Maximum 200 words) This training grant for 5 predoctoral students was designed to integrate students in diverse disciplines with a common interest in understanding breast cancer. The special features of this training grant was proposed to be a journal club designed to facilitate the exchange and discussion of current literature and research in breast cancer, the initiation of a yearly retreat to encourage interactions between breast cancer training grant participants, and the initiation of a special seminar series involving a guest speaker prominent in the field of breast cancer research. The Breast Cancer Training Grant has been successfully implemented and has supported 5 excellent students for the past year. Four abstracts, 3 publications, and a submitted manuscript related to breast cancer resulted from this support. The monthly journal clubs proved to be excellent opportunities to become acquainted with the breast cancer-related work performed by members of the group as well as in the literature. The opportunity to meet the visiting seminar speaker was judged a valuable experience. Support for attendance at a national meeting was administered in lieu of the retreat, and the Breast Cancer Program Retreat for 1995 is planned for September 9. There has been excellent progress on the aims of this grant.			
14. SUBJECT TERMS Training grant, breast cancer		15. NUMBER OF PAGES 7	
		16. PRICE CODE	
17. SECURITY CLASSIFICATION OF REPORT Unclassified	18. SECURITY CLASSIFICATION OF THIS PAGE Unclassified	19. SECURITY CLASSIFICATION OF ABSTRACT Unclassified	20. LIMITATION OF ABSTRACT Unlimited

FOREWORD

Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the US Army.

Where copyrighted material is quoted, permission has been obtained to use such material.

Where material from documents designated for limited distribution is quoted, permission has been obtained to use the material.

Citations of commercial organizations and trade names in this report do not constitute an official Department of Army endorsement or approval of the products or services of these organizations.

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).

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

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

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

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

Accession For	
HTIS GRA&I	<input checked="" type="checkbox"/>
DTIC TAB	<input type="checkbox"/>
Unannounced	<input type="checkbox"/>
Justification	
By _____	
Distribution/Availability	
Availability Codes	
Dist	Avail and/or Special
A-1	

[Signature] 6/28/95
PI - Signature Date

TABLE OF CONTENTS

	Page
Front Cover	
Report Documentation Page	2
Foreword	3
Table of Contents	4
Introduction	5
Progress	5
Conclusions	7
References	7
Appendix	7

INTRODUCTION

This training grant for 5 predoctoral students was designed to integrate students in diverse disciplines with a common interest in understanding breast cancer. The special features of this training grant was proposed to be a journal club designed to facilitate the exchange and discussion of current literature and research in breast cancer, the initiation of a yearly retreat to encourage interactions between breast cancer training grant participants, and the initiation of a special seminar series involving a guest speaker prominent in the field of breast cancer research.

PROGRESS

Students:

The following five students were supported by the Breast Cancer Training grant between June 1, 1994 to May 31, 1995. Listed is the accomplishments in the form of publications or abstracts for each student during this time.

Mark Alexandrow. Third/fourth year student, laboratory of Harold L. Moses, Dept. of Cell Biology. Progress on this grant is demonstrated by the following abstract, review article, and submitted manuscript.

Alexandrow, M.G. and H.L. Moses, "Late-G1 effects of c-myc on TGF β 1-induced inhibition of mouse keratinocytes". presented at Keystone Symposium "Oncogenes: 20 years later", Jan, 1995.

Alexandrow, M.G., and H.L. Moses "Transforming growth factor β and cell cycle regulation". Cancer Res. 55: 1452-1457, 1995

Alexandrow, M.G., and Moses, H.L. "TGF β 1 inhibits mouse keratinocytes late in G1 independent of effects on gene transcription" submitted

Renee Bailey. Second/third year student, laboratory of Fritz Parl, Dept. of Pathology. Progress on this grant is demonstrated by an abstract submitted to The Endocrine Society entitled

Bailey, L.R., Yee, C.J., Verrier, C.S., Roodi, N., and Parl, F.F., "Estrogen induction of WAF1/Cip1 in MCF-7 breast cancer cells by a p53-independent pathway".

Mike Engel. MSTP student, First/second year of graduate training, laboratory of Harold L. Moses, Dept. of Cell Biology. Research progress during this grant period is summarized in the following paragraphs.

Considerable effort was directed toward identifying signal transducing proteins in the TGF- β receptor signaling pathway. Two candidate proteins were detected by a yeast interaction-trap screening of a HeLa cell library with the cytoplasmic domain of the type I

TGF- β receptor (Alk-5). The first protein, known as FKBP12, is a member of the immunophilin class of cytoplasmic proteins and derives its name from its ability to coordinate the interaction between the immunosuppressive agent FK-506 and its target phosphatase, calcineurin. Based upon the data from the yeast two-hybrid screen and supportive data from an in vitro binding assay, it was hypothesized that FKBP12 might play a role in transduction of growth inhibitory or immunosuppressive signals by TGF- β . However, the interaction was not detectable in vivo.

The second candidate protein identified in the interaction trap screen was the α -subunit of the heterodimeric enzyme farnesyl transferase. This enzyme plays an essential role in the isoprenylation of various substrates, including p21-ras, nuclear lamins A and C, and the β -subunits of heterotrimeric G- proteins. The potential role of this enzyme in TGF- β mediated signal transduction both in vitro and in vivo was explored. While in vitro data with regard to this relationship is promising, an in vivo relationship of either an interactive or functional nature has not been demonstrated.

Recently, issues related to the specificity of signal transduction by the TGF- β receptor and other members of this receptor family such as the activin and BMP receptor complexes has been investigated. It is of interest to know to what degree disruption of one signaling pathway, for example by the introduction of dominant negative constructs, interferes with signal transduction by other receptor family members. Furthermore, the inducible transcription systems can be used to quantitatively assess receptor "cross talk" if it exists.

Laura J. Niedernhofer, MSTP student, second/third year of graduate training, laboratory of Larry Marnett, Dept. of Biochemistry.
Progress on this grant is summarized by an abstract presented at the Eighth International Conference on Carcinogenesis and Risk Assessment.

Niedernhofer, L.J., Chaudhary, A.J., and Marnett, L.J. "Mutagenicity of Malondialdehyde in Human Cells".

Cindy J. Yee. Second/third year student, laboratory of Fritz Parl, Dept. of Pathology.
Progress on this grant is demonstrated by two manuscripts and an abstract.

C.J. Yee, N. Roodi, C.S. Verrier, and F.F. Parl. "Microsatellite instability and loss of heterozygosity in breast cancer". *Cancer Res.* 54: 1641-1644, 1994.

N. Roodi, L.R. Bailey, W-Y Kao, C.S. Verrier, C.J. Yee, W.D. Dupont, and F.F. Parl. "Estrogen receptor analysis in estrogen receptor-positive and receptor-negative primary breast cancer". *J. N.C.I.* 87: 446-451, 1995.

C.J. Yee, C.S. Verrier, L.R. Bailey, N. Roodi, and F.F. Parl, "Molecular characterization of lobular breast cancer". abstract presented at the 86th Annual Meeting of the American Association for Cancer Research, Toronto, Canada

Journal Club

The Breast Cancer Training Grant met monthly in the Vanderbilt Cancer Center Conference Room. The original plan to meet bimonthly was altered to a monthly meeting in view of the active seminar series supported by the Vanderbilt Cancer Center which meets on a weekly basis. Each student presented either a research seminar on their own work, or a topic of current interest to the group. Laura Rudolph, a predoctoral student supported by an individual training grant for the Dept. of the Army Breast Cancer Research Initiative also participated in this journal club. In addition, a faculty member and an outside speaker were invited to present their research during this time.

Retreat

The retreat for the Breast Cancer Training Program is held in conjunction with the retreat for the Breast Cancer Program for the Vanderbilt Cancer Center. In 1994 this retreat was held on the Vanderbilt campus in June and there was insufficient time to include the Breast Cancer Training Grant participants. In 1995 the retreat will be held September 9 at Montgomery Bell State Park and all Breast Cancer Training Grant grantees are expected to attend and present a poster. For the 1994 year, we supported the travel of two trainees to attend the annual meeting of the American Association of Cancer Research and the Endocrine Society meeting to present posters.

Seminar speaker

The Breast Cancer Training Grant supported the visit of Dr. Bill Muller, McMaster University, on May 25, 1995. Dr. Muller presented an excellent seminar on his recent work using a transgenic mouse mouse system to study signal transduction in mammary carcinogenesis. The Breast Cancer Training Grant students met with Dr. Muller over lunch following the seminar. There was considerable interest and excitement over the work presented and this proved to be a very valuable training opportunity for the students.

CONCLUSIONS

The Breast Cancer Training Grant has been implemented and has supported 5 excellent students for the past year. Four abstracts, 3 publications, and a submitted manuscript with relevance to breast cancer resulted from this support. The monthly journal clubs proved to be excellent opportunities to become acquainted with the breast cancer-related work performed by members of the group as well as in the literature. The opportunity to meet the visiting seminar speaker was judged a valuable experience. The Breast Cancer Program retreat was not accomplished this past funding period but is planned for September, 1995.

REFERENCES - Not Applicable

APPENDIX - Not Applicable