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This training grant for 5 predoctoral students was designed to integrate students in diverse disciplines with a common interest in understanding breast cancer. The training features of this program are 1) a monthly journal club to facilitate the exchange of current information related to breast cancer research, 2) a yearly retreat to encourage interactions between trainees and investigators at Vanderbilt University interested in Breast Cancer research, and 3) a special seminar series involving a guest speaker prominent in the field of breast cancer research. There were changes in the yearly retreat mechanism of training which is described below. Other goals were accomplished over the past year. Two trainees were supported for a third year, two trainees for a second year, and one new trainee was supported by this training grant; three different departments are represented. Five abstracts, 5 submitted manuscripts, and 1 manuscript in press related to breast cancer resulted from this support.

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

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FOREWORD

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____ 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).

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PI Signature 7/30/97 Date

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ARMY BREAST CANCER TRAINING GRANT DAMD17-94-J-4024
Annual Report for 1996-1997 fiscal year

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 the training grant were a monthly journal club, a yearly retreat, and the invitation of a seminar speaker prominent in the field of breast cancer research. These mechanisms were designed to provide students with opportunities to enhance their own research by stimulating communication with investigators at Vanderbilt interested in Breast Cancer research, increasing their knowledge of current literature in the field, and exposing them to the latest research from prominent investigators at other institutions. Trainees are required to successfully complete the Cancer Biology course (4 credits, CBIO 342). Progress is measured by the presentation of original research in the form of abstracts and publishable manuscripts.

PROGRESS:

Students:

The following five students were supported by the Breast Cancer Training Grant between June 1, 1996 to May 31, 1997. Listed is the accomplishments in the form of required coursework completed, abstracts, and publications for each student during this time.

Renee Bailey. Fourth/fifth year student in the laboratory of Dr. Fritz Parl, Dept. of Pathology. Reappointed to the training grant for a third year based on excellent progress and high relevance to breast cancer. Progress is demonstrated by a first-author publication submitted to Cancer Research, participation in two other manuscripts submitted or in press, and two abstracts. The work represented by the abstract by Bailey et al was presented at the American Association for Cancer Research annual meeting in San Diego in April, 1997 and was also presented at the Vanderbilt University Cancer Center retreat held in June, 1997.

Bailey, L.R., Roodi, N., Verrier, C.S., Yee, C.J., Dupont, W.D., and Parl, F.F. 1997. Breast cancer and CYPIA1, GSTM1, GSTT1 polymorphisms: evidence of a lack of association in Caucasians and African Americans. Cancer Research, (submitted).

Yee, C.J., Roodi, N., Bailey, L.R., Verrier, C.S., Pietenpol, J.A., and Parl,F.F. 1997.
Characterization of a putative p53 binding site in the 5'upstream region of the estrogen receptor (ER) gene: ER is not a p53 target gene. Cell Growth & Differentiation, (submitted).

Verrier, C.S., Roodi, N., Yee, C.J., Bailey, L.R., Jensen, R.A., Bustin, M., and Parl, F.F. 1997. High mobility group protein HMG-1 and TBP-associated factor

TAFII30 affect estrogen receptor-mediated transcriptional activation. Molecular Endocrinology, (in press for July).

Verrier, C.S., Roodi, N., Yee, C.J., Bailey, L.R., Jensen, R.A., ustin, M.,and Parl, F.F.1997. High mobility group protein HMG-1 and TBP-associated factor TAFII30 affect estrogen receptor-mediated transcriptional activation. Program and Abstracts for the Endocrine Society.

Bailey, L.R., Roodi, N., Verrier, C.S., Yee, C.J., Dupont, W.D., and Parl, F.F. 1997. Breast cancer and CYPIA1, GSTM1, GSTT1 Polymorphisms:evidence of a lack of association in Caucasians and African Americans. Proceedings of the American Association for Cancer Research, 38: 214.

Heather Joseph. Third/forth year student, laboratory of Dr. Harold Moses, Dept. of Cell Biology. Reappointed for a second year on the Training Grant due to good progress and relevance to breast cancer. Progress is summarized by the following manuscript which has been submitted for publication.

Joseph, H., Moses, H.L., and Serra, R. 1997. Overexpression of a kindase deficient TGF-beta type II receptor in mouse mammary stroma results in increased epithelial branching. Submitted

Suzanne Szak. Third/fourth year student, laboratory of Dr. Jennifer Pietenpol, Dept. of Biochemistry. Reappointed to training grant for a second year due to good progress and participation in training grant functions. Progress is summarized by an abstract presented at the American Association of Cancer Research Workshop on Molecular Biology and Pathology of Neoplasia and is the topic of a manuscript in preparation.

Szak, S. T., and Pietenpol, J.A. P53 binding to DNA lesions: A Biochemical Analysis. Manuscript in preparation.

Cindy J. Yee. Fourth/fifth year student, laboratory of Dr. Fritz Parl, Dept. of Pathology. Reappointed to training grant for a third year based on excellent progress in areas highly relevant to breast cancer. Progress on this grant is demonstrated by a first author publication submitted to "Oncogene", and participation on two other manuscripts submitted or in press and two abstracts.

Yee CJ, Roodi N, Bailey LR, Verrier CS, Pietenpol JA, and Parl FF. Identification and Functional Analysis of a Putative p53 Binding Site in the Upstream Region of the Estrogen Receptor (ER) Gene. Submitted to Oncogene.

Verrier CS, Roodi N, Yee CJ, Bailey LR, Jensen RA, Bustin M, and Parl FF. High Mobility Group Protein HMG-1 and TBP-Associated Factor TAFII30 Affect Estrogen

Receptor-Mediated Transcriptional Activation. In press Molecular Endocrinology (July 1997).

Bailey LR, Roodi N, Verrier CS, Yee CJ, Dupont WD, and Parl FF. Breast Cancer and CYPIA1, GSTM1, GSTT1 Polymorphisms: Evidence of a Lack of Association in Caucasians and African Americans. Submitted to Cancer Research.

Verrier CS, Roodi N, Yee CJ, Bailey LR, Jensen RA, Bustin M, and Parl FF. High Mobility Group Protein HMG-1 and TBP-Associated Factor TAFII30 Affect Estrogen Receptor-Mediated Transcriptional Activation. Program and Abstracts for the Endocrine Society.

Bailey LR, Roodi N, Verrier CS, Yee CJ, Dupont WD, and Parl FF. Breast Cancer and CYPIA1, GSTM1, GSTT1 Polymorphisms: Evidence of a Lack of Association in Caucasians and African Americans. Proceedings of the American Association for Cancer Research, 38: 214.

Rebecca Townsend. First/second year student in the laboratory of Harold L. Moses, Dept. Of Cell Biology. Successfully completed 4 credit hours of coursework in "Cancer Biology", CBIO 342. Her project and progress to date is summarized below.

In humans, BRCA1 mutations suggest a predisposition to inherited and sporadic breast and ovarian cancers. BRCA1 is thought to act as a tumor suppressor gene. Transgenic mice containing a naturally occuring splice variant of the human BRCA1 gene were generated under the control of the mouse mammary tumor virus (MMTV) promoter/enhancer, which directs expression to the mammary gland. Expression of this human BRCA1 splice variant results in a hyperplasia of the ductal system, which is opposite of the effect of other tumor suppressors on the mouse mammary gland.

Journal Club

The Breast Cancer Trainees continued to meet monthly in the Vanderbilt Cancer Center Conference room in conjunction with the Breast Cancer Program of the Vanderbilt Cancer Center. The schedule of the meetings was determined by the Principal Investigator of the Training Grant (Lynn Matrisian, Ph.D.) and the Program Leader of the Breast Cancer Program (Carlos Arteaga, M.D.). The format this year was to alternate between current research presentations by Breast Cancer Program faculty members or advanced students (ie. R. Bailey), and discussion sessions lead by more junior students participating in theTraining Grant with assistance from a designated faculty member. In each of the discussion sessions, each student was assigned 1-2 publications to summarize and present to the group. The student discussion presentations were as follows: "Mechanisms of Antiestrogen Resistance (C. Yee, December, 1996), "Cell Cycle in Breast Cancer" (S. Szak, February, 1997), "The IGF system in Breast Cancer" (H. Joseph, April, 1997), and "Transgenic Models of Breast Cancer" (R. Townsend, May, 1997). Meetings were well attended and discussion was lively.

Retreat

The Breast Cancer Retreat held in previous years was a function supported by the Breast Cancer Program of the Vanderbilt Cancer Center and included participation by trainees of this Army Training Grant. In 1996, Lynn Matrisian resigned her position as Program Leader of the Breast Cancer Program to take the position of Associate Director for Education of VCC. Carlos Arteaga assumed the position of Program Leader. A decision was made to discontinue the yearly Breast Cancer Retreat and to include faculty presentations in the monthly Jounral Club which was viewed as a very successful venue for interaction. In addition, the VCC has started an Annual Retreat on the Vanderbilt campus which was held in June, 1997. This forum gave several of the students an opportunity to present their recent work in poster form to receive input from the VCC community in general.

Seminar Speaker

Due to Vanderbilt University-mandated increases in student stipend, funds available for a seminar speaker were reduced. However, the Army Training Grant participated in the visit of Dr. Allen Oliff of Merck Pharmaceuticals on April 10, 1997. Dr. Oliff gave a general presentation on the process of Drug Discovery and Implementation, using *ras* farnsyltransferase inhibitors as an example. Although this topic is not specifically related to breast cancer, it was important for students being trained in cancer research to appreciate the complexities of the ultimate goal of their work - the treatment and cure of cancer. Dr. Oliff gave an excellent presentation, including an example of how transgenic mice with oncogenes targeted to the mammary gland can be an excellent model for drug testing. In addition, he was available to answer questions from students in an informal lunch-time gathering following his seminar. This was a valuable experience for many students since they have little exposure to investigators from the pharmaceutical industry at this stage of their career.

CONCLUSIONS:

The third year of the Breast Cancer Training Grant supported 1 new student, 2 students for a second year, and 2 students for a third year from the Departments of Cell Biology, Pathology, and Biochemistry. Select students were reappointed to the training grant based on excellent research productivity in areas highly relevant to breast cancer. Research productivity is demonstrated by a total of 5 abstracts and 7 manuscripts during this period. The Breast Cancer Journal Club provided an excellent forum for discussing current literature on topics of particular relevance to breast cancer research with local experts and for becoming informed of current research in Breast Cancer at Vanderbilt. The invitation of Dr. Allen Oliff to present insights into the process of drug development enhanced student appreciation for the ultimate goal of their research - the treatment of cancer. Training of these students was therefore enhanced at multiple levels contributing to their scientific development.

REFERENCES: not applicable

APPENDIX: not applicable