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The goal of the present proposal is to provide post-doctoral training opportunities in breast cancer research that focus on the role of microenvironment in mammary gland biology. Trainees will benefit from working in a dynamic interactive program under the guidance of the LBNL mentors to investigate the intersection of hormone action, growth factor activity and extracellular matrix remodeling during mammary gland development and carcinogenesis. In addition, trainees will be exposed to a variety of other topics related to breast cancer, as well as research ranging from molecular medicine to genomics, by their participation in working groups, lectures and scientific meetings with other Berkeley Lab and Bay Area researchers.

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Introduction

The goal of the present proposal is to provide post-doctoral training opportunities in breast cancer research that focus on the role of microenvironment in mammary gland biology. Trainees will benefit from working in a dynamic interactive program under the guidance of the LBNL mentors to investigate the intersection of hormone action, growth factor activity and extracellular matrix remodeling during mammary gland development and carcinogenesis. In addition, trainees will be exposed to a variety of other topics related to breast cancer, as well as research ranging from molecular medicine to genomics, by their participation in working groups, lectures and scientific meetings with other Berkeley Lab and Bay Area researchers.

Recruitment

As reported in 2001, applicants for the postdoctoral fellowships were recruited by posting advertisements at major cancer meetings, on mammary biology lists and through the Lawrence Berkeley National Laboratory Human Resources webpage. In additional, personal contacts and unsolicited applicants to individual mentors were considered for these positions.

- American Association of Cancer Research posting
- LBNL web posting: Initial #13392, Ongoing #13447; Web address: http:cjo.lbl.gov/
- Posted to Mammary Biology List (maintained by P. Neville at the University of Colorado)

The text of the posting was as follows:

> Several postdoctoral training positions are available to study mammary biology and breast cancer using human and mouse mammary cell culture and animal models. Fellows will conduct a research project defined by collaboration of two mentors in a DOD –BCRP funded postdoctoral training program. Research areas include growth factor biology and signaling, mechanisms of differentiation, senescence and neoplastic progression, radiation biology, cell-cell and cell-extracellular matrix interactions, tumor biology, and hormone action.
>
> Requirements: Recent Ph.D. in cell and molecular biology or related field. Ability to work with guidance of principal investigator and collaborators. Ability to conduct experiments independently, maintain appropriate records and manage data. Excellent verbal and written communication.

Screening and Selection

As indicated in 2001, approximately 20 applicants responded. Their letters and CVs were circulated to the mentor groups. Mentors then indicated their enthusiasm for individual applicants, who were invited to LBNL to present their current research. Mentors interviewed applicants and discussed possible research projects. Candidates were informed at the time that their research projects would be the result of collaboration between at least two mentors. Three candidates were recruited.

Postdoctoral Fellows 2000-2001

- Ana Erickson, Ph.D.

Dr. Erickson joined the Barcellos-Hoff lab in June 2001 to conduct research on a joint project with Dr. Barcellos-Hoff and Bissell. She obtained her degree in Cell Biology from the University of Alabama at Birmingham in 2001 in the laboratory of Dr. John Couchman. Her expertise in proteoglycan biology and molecular biology provides an excellent background for her current project to study the underlying molecular mechanisms controlling the expression of E-cadherin in irradiated human mammary cells. Her project is to examine E-cadherin mRNA, protein abundance and localization, and its association with other membrane and cytoskeletal proteins in cells surviving radiation exposure in the three-dimensional model of alveolar morphogenesis.

We have previously reported that non-malignant HMT-3522 human breast cancer population, S1, that are cultured within an extracellular matrix and treated with TGF-β1 and radiation (2 Gy) produce daughter cells that exhibit dysfunctional cell-cell and cell-ECM interactions. The acinar colonies analyzed with immunofluorescence and confocal microscopy exhibit decreased E-cadherin and connexin 43. The loss of these proteins and the resulting disorganized morphology are consistent with malignant progression. To understand this phenotype we focused on the basis for the loss of E-cadherin. Monolayer cultures of S1 cells were analyzed 10 days after being irradiated and cultured +/- TGF-β; unirradiated S1 cells served as controls. The progeny of the irradiated cells appeared morphologically similar to unirradiated cells. TGF-b treatment induced a 'scatter' morphology in both control and irradiated cultures. TGF-β1 treatment of both resulted in reduced E-cadherin and β-catenin protein as measured by Western blot analysis, which was reflected by reduced mRNA abundance as shown by quantitative RT-PCR. Immunofluorescence localization of E-cadherin and β–catenin was greatly compromised in TGF-b-treated irradiated cells even though Western blot analysis indicated similar protein abundance. Immunoprecipitation for E-cadherin revealed that less E-cadherin is associated with the cytoskeleton in dual-treated cells compared to cells treated with TGF-β1 alone. The cytoskeleton of the irradiated cells also showed significant alterations as evidenced by significantly increased vimentin. These results suggest that TGF-β1 affects E-cadherin expression but radiation affects its association with the cytoskeleton. Importantly, this effect of radiation is heritable and could contribute to its action as a carcinogen in breast.

Dr. Erickson and Dr. Barcellos-Hoff have a review for Expert Opinion in press on the utility of therapeutic targeting of stroma and extracellular matrix in breast cancer. She presented her research findings at the Era of Hope Meeting in Orlando, Florida in September, 2002 and will also present them at the American Society of Cell Biology in December, 2002 in San Francisco. In addition she attended the California Breast Cancer Research Meeting in Oakland, CA in March, 2002 and the American Cancer Society Meeting in San Francisco in April, 2002.

- Rana Zahedi, Ph.D.

Dr. Zahedi joined Dr. Bissell's laboratory in 2000 as a senior Postdoctoral Fellow. She obtained her Ph.D. in Protein Chemistry/Toxicology in 1996 at the University of Paris VII, Paris, France. She conducted postdoctoral training from 1997-2000 at The Center for Blood Research, Harvard Medical School, Boston, Massachusetts. Her research project involved identification the

putative membrane bound protease necessary for cleaving epimorphin. The activated protease is postulated to cleave and release the soluble form of epimorphin, which apolar presentation to mammary epithelial cells mediates alveolar formation. She worked on determining the properties of the protease that cleaves epimorphin, and further purifying and identifying the protease to analyze the consequences of its over-expression or repression of the identified in culture and in vivo. Dr. Zahedi received her own grant from the Department of Defense Breast Cancer Research Program and was replaced on the project by Dr. Norisa Uehara in December 2001.

- Norisa Uehara, Ph.D.

Dr.Uehara joined Dr. Shyamala's laboratory in April 2001 and was appointed on the training grant in December 2001. He obtained his Ph.D degree in Genetic Resources Technology with Dr. Shirahata in Division of Bioresources and Bioenviromental Sciences from the Kyushu University, Japan. The focus of his research project is on the role of progesterone receptors in mammary development and neoplasia, using various genetically engineered mouse models. In particular, he will characterize the various mammary phenotypes using specific molecular markers implicated in transformation and its progression. His previous training the field of cellular senescence and his expertise in molecular biology is well suited to his current project, as a result of which he has made considerable progress. Part of his research was presented at 2002 Annual meetings of AACR and The Endocrine Society(abstracts enclosed) and is a co-author in two manuscripts, currently under revision.

- Scott Jepson, Ph.D.

Dr. Jepson worked in the laboratory of Dr. Yaswen from June 2001 through April 2002 before leaving to accept a job in a biotechnology firm in the United Kingdom. While in Dr. Yaswen's lab, Scott used human mammary epithelial cells (HMEC) to study p53 function during immortalization and radiation exposure, to examine p53-dependent pathways that influence telomerase expression, and to determine whether p53 responsiveness of normal/immortal HMEC is modulated by the cytokine TGFb. In immunoblotting experiments, Scott was able to measure differences in the levels of specific phosphorylated forms of p53 in HMEC at different stages of immortalization. He performed quantitative RT-PCR and found that higher hTERT mRNA levels correlated with increased telomerase activity in HMEC undergoing immortalization, and in conditionally immortal HMEC exposed to a dominant negative inhibitor of p53 function. He performed experiments to determine whether p53 directly influenced telomerase activity, as had previously been reported, but found no effect of purified p53 or a competing peptide on telomerase activity in immortalized HMEC. Additional electromobility shift assays, co-immunoprecipitation experiments, and chromatin immunoprecipitation (ChIP) experiments were performed to examine the interaction of p53 with Sp1, a transcription factor crucial for hTERT promoter function. These latter experiments, while suggestive, were inconclusive, and will require further optimization.

- Joanna E. Mroczkowska-Jasinska, Ph.D.

Dr. Mroczkowska-Jasinska joined the lab of Dr. Yaswen in June 2002. She obtained her doctoral degree in 1999 from the Department of Molecular and Cellular Neurobiology at the Nencki Institute of Experimental Biology, Polish Academy of Sciences in Warsaw, Poland. She briefly conducted postdoctoral training in the laboratory of Dr. Ruth Lupu at LBNL studying functional sites of the erbB-2 receptor and its activator heregulin, before Dr. Lupu moved her

laboratory to Chicago. Dr. Mroczkowska-Jasinska is currently studying pathways that influence telomerase expression in human mammary epithelial cells, and the influence of p53 and TGFb on these pathways. These studies are in collaboration with Dr. Barcellos-Hoff.

Training Activities

The trainees are exposed to a wide range of research approaches, tools, and methods that are encompassed in the mentor's laboratories. In addition to weekly **laboratory meetings** with the preceptor, a monthly **Cell and Molecular Biology department meeting** is held to bring together the investigators and the trainees to discuss research and literature relevant to the program. The department will host a Postdoctoral Research Day on December 5 that will feature poster presentations and a speaker chosen by postdoctoral fellows. **Division seminars** are held weekly (see Attachment 1 consisting of a roster of speakers for 2000-2002).

Of particular relevance is the monthly **Mammary Gland Affinity Group**, which is a long standing tradition. LBNL mammary biology and breast cancer groups meet for informal research presentations. Additional participants from UC San Francisco Medial Center and UC Berkeley campus attend regularly. Approximately 30-40 participate. The format consists of two short talks by postdoctoral fellows.

The Life Sciences Division currently hosts approximately 50 research grants in breast cancer and mammary biology, totaling over $16 million in funds. We are pleased with the recent establishment of a laboratory wide program entitled, **The Breast Cancer Research Awareness Forum,** held monthly for a general audience highlighting research at LBNL. Dr. Mina Bissell, the Principal Investigator of the Training Grant, chairs these sessions. The first forum, on August 23, 2001, was on the role of hormones in breast cancer prevention and treatment and featured Susan Love, M.D., Adjunct Professor of Surgery at the University of California, Los Angeles and Satyabrata Nandi, Ph.D., Professor of Cell and Developmental Biology, University of California, Berkeley. The second forum, held on September 10, 2001, featured Berkeley Lab's Mary Helen Barcellos-Hoff, Ph.D. Head of the Lawrence Berkeley National Laboratory's Life Sciences Cancer and Tissue Biology Group, and Bill Moses, Ph.D., Senior Staff Physicist in LBNL's Department of Functional Imaging. Their discussion provided an overview of Life Sciences Division's breast cancer research activities, from molecular, cellular and radiation biology to the development of new compact and ultra sensitive imaging devices for the detection of breast cancer. David Irwin, M.D., Director of Clinical Research at the Alta Bates Comprehensive Cancer Center in Berkeley and Berkeley Lab employee Ms. Sonia Mueller presented the October, 2001 forum on Clinical Trials. Ms. Mueller brought a patient's perspective to the event. In November 2001, Debu Tripathy, Ph.D., Associate Clinical Professor of Medicine at the University of California at San Francisco, provided the overview of research & a scientific context while Berkeley acupuncturist, Isaac Cohen, M.D., spoke on Alternative Therapies. On January 13, 2001, Mina J. Bissell, Ph.D., Director of the Life Sciences Division at Lawrence Berkeley National Laboratory presented a special forum entitled "Breast Cancer Research: New Models for the Millennium." Dr. Bissell, who was named one of five recipients of an "Innovator Award" from the Department of Defense Breast Cancer Research Program, discussed the significance of the Innovator Award relative to her breakthrough research on the

cellular microenvironment. Mary Helen Barcellos-Hoff, head of the Cell and Tissue Biology Group in the Life Sciences Division, and Catherine Park, M.D., Assistant Clinical Professor in the Department of Radiation Oncology at the University of California, San Francisco presented the May 2002 forum, which explored how mammary gland growth is regulated in response to radiation. The June 2002 forum featured Dr. Judith Campisi, Berkeley Lab Senior Scientist, and Christopher Benz, M.D. of the Buck Institute, whose presentations focused on breast cancer and aging. These forums have been very well received and continue to generate enormous interest and participation. Subsequent forums will continue to investigate other emerging breast cancer surgery and treatment options. The forums are an important avenue for postdoctoral fellows to learn not only about research but also how to communicate about their research with a lay audience.

Reportable Outcomes

Anna C. Erickson, William S. Chou, Rhonda L. Henshall-Powell, Mina J. Bissell and Mary Helen Barcellos- Hoff: Radiation Alters Cytoskeletal Association of E-cadherin in TGF-β Human Mammary Epithelial Cells. American Association for Cell Biology, San Francisco, CA December, 2002.

Anna C. Erickson, William S. Chou, Rhonda L. Henshall-Powell, Mina J. Bissell and Mary Helen Barcellos-Hoff: The Progeny of Irradiated Human Mammary Epithelial Cells Exhibit a Distinct Phenotype in Response to Transforming Growth Factor-β1. Era Of Hope, Orlando, FL, September, 2002.

Erickson, A.C. and M.H. Barcellos-Hoff: The not-so innocent bystander: Microenvironment as a therapeutic target in cancer. **Expert Opinion** Accepted, 2002.

Please see attached abstracts.

Attachment 1 Roster of Speakers List for 2001-2002

DATE		SPEAKER	AFFILIATION
2001			
JAN	9	Martin McMahon	University of California, San Francisco
19		Satyabrata Nandi	University of California, Berkeley
30		Gene E. Robinson	University of Illinois
FEB	6	Ross C. Hardison	The Pennsylvania State University
13		Marc Vidal	Harvard Medical School
15		Grant T. Gullberg	University of Utah
20		Christopher Benz	Buck Institute for Age Research
27		Gene Meyers	Celera Genomics
MAR	6	Anita B. Roberts	National Institutes of Health
15		Eva Y.-H.P. Lee	University of Texas Health Science Center
16		Thomas A. Steitz	Yale University
19		Ed Roos	The Netherlands Cancer Institute
20		Tej Pandita	Columbia University
28		Jan Vijg	Institute for Drug Development
29		William J. Muller	McMaster University
APR	5	Catherine L. Peichel	Stanford University
10		Robert J. Lechleider	Uniformed Services Univ. of the Health Sciences
17		Leona D. Samson	Harvard University School of Public Health
18		Claudia Gravekamp	San Antonio Cancer Center
MAY	1	Charles E. Samuel	University of California, Santa Barbara
8		Mary Ann Osley	University of New Mexico
15		Graham C. Walker	Massachusetts Institute of Technology
22		Michael Levine	University of California, Berkeley
23		H. Steven Wiley	Pacific Northwest National Laboratory
31		Mats Gustafsson	University of California, San Francisco
JUN	5	Martin Caffrey	The Ohio State University
12		Susan J. Fisher	University of California, San Francisco
AUG	29	Nora Volkow	Brookhaven National Laboratory
SEPT	18	Barbara Meyer	University of California, Berkeley
18		Helen Hobbs	University of Texas Southwestern Medical Center
25		Anat Biegon	Lawrence Berkeley National Laboratory
OCT	2	William Jagust	University of California, Davis, Medical Center
9		Mina Bissell	Lawrence Berkeley National Laboratory
16		John Reinitz	SUNY Stonybrook
23		Gordon Hager	National Institutes of Health
30		Edward Rubin	Lawrence Berkeley National Laboratory
NOV	6	Gary Karpen	The Salk Institute
13		John Gerdes	Central Washington University
27		Christi Walter	University of Texas Health Science Center
DEC	4	Martin Kreitman	University of Chicago
11		James Haber	Brandeis University

DATE	SPEAKER	AFFILIATION
2002		
JAN 1		
8	Beverly Emerson	The Salk Institute
15	David Haussler	University of California, Santa Cruz
22	James Shull	University of Nebraska Medical Center
29	Steve Kowalczykowski	University of California, Davis
FEB 5	Mark Groudine	Fred Hutchinson Cancer Center
12	Saraswati Sukumar	The Johns Hopkins University School of Medicine
19	Carl Anderson	Brookhaven National Laboratory
26	Eric Wright	University of Dundee
MAR 5	Marit Nilson-Hamilton	Iowa State University
12	Bridget Carragher	University of Illinois, Urbana-Champaign
19	Steve Elledge	Baylor College of Medicine
26	Vicki Lundblad	Baylor College of Medicine
APR 2	Peter St. George-Hyslop	University of Toronto
9	Steven Larson	Memorial Sloan-Kettering Cancer Center
16	Joan Fox	Cleveland Clinic Foundation
23	Tracy Handel	University of California, Berkeley
30	Svante Paabo	Max-Planck-Institute of Evolutionary Anthropology
MAY 7	Sanjiv Gambhir	University of California, Los Angeles
14	Steve Baylin	The Johns Hopkins University School of Medicine
21	Bing Jap	Lawrence Berkeley National Laboratory
28	Priscilla Cooper	Lawrence Berkeley National Laboratory
JUN 4	David Hovda	University of California, Los Angeles
11	Joseph DeRisi	University of California, San Francisco
SEP 10	William Morgan	University of Maryland
OCT 1	Nathaniel Heintz	Rockefeller University
8	Ron Frostig	University of California, Irvine
15	Mary Helen Barcellos-Hoff	Lawrence Berkeley National Laboratory
22	Susan Wallace	University of Vermont
29	Joel Hirschhorn	Children's Hospital Boston
Nov 5	Eric Wright	Ninewells Hospital and Medical School
12	Stephen Ethler	University of Michigan
26	Klaus Schulten	University of Illinois at Urbana-Champaign
Dec 3	Thomas Kunkel	NIEHS, NIH
10	Lawrence Donehower	Baylor College of Medicine
19	William Brinkley	Baylor College of Medicine

Norihisa Uehara, PhD **(Refer to this abstract as # 107144)**

Lawrence Berkeley National Laboratory

1 Cyclotron RD

Berkeley, CA 94720

USA

Involvement of Id genes in Mammary Development and its implications to carcinogenesis

Norihisa Uehara, Yu-Chien Chou, Jose Galvez, Robert Cardiff, Shyamala Gopalan, Lawrence Berkeley National Laboratory, Berkeley, CA; University of California, Davis, Davis, CA.

Id proteins belong to a subfamily of helix-loop-helix (HLH) proteins and regulate cell functions primarily by dimerization with other transcriptional regulators, principally basic HLH proteins. There is extensive documentation that Id proteins promote cell proliferation and negatively regulate differentiation, and this phenomenon has been demonstrated with regard to the expression of Id-1 in a non-tumorigenic mammary epithelial cell line (SCp2). Normal mammary glands consist of myoepithelial cells and luminal epithelial cells and it is the luminal cell that is primarily targeted for proliferation, differentiation and carcinogenesis. Therefore, to assess the precise significance of Id-1 in mammary biology and its significance to carcinogenesis, we examined its cellular localization in vivo. We report that Id-1 expression is associated with myoepithelial cells and not luminal epithelial cells. To our knowledge, this represents the first transcriptional regulator to be identified in myoepithelial cells. In addition to Id-1, we also examined Id-3 expression. In normal mammary glands Id-3 is expressed in luminal epithelial cells but at a very low level, while it is overexpressed in mammary epithelial cells of progesterone receptor A (PR-A) transgenic mice, which exhibit hyperproliferation. Overexpression of Id-3 in PR-A transgenics is not simply tied to the hyperproliferation of epithelial cells, since this does not occur in the glands of early pregnant wild type mice, when there is a massive increase in epithelial cell proliferation. Based on these observations, we propose that the function of Id proteins in mammary glands is context dependent both with regard to the cell type and the family

member. As such, the expression of Id-1 in myoepithelial cells, which represent a mitotically quiescent population, is clearly not tied to cell proliferation, which supports the emerging concept that Id proteins may have wide biological roles. On the other hand, the low level of Id-3 expression in normal mammary gland and its over expression in mammary gland of PR-A transgenics suggest that in luminal epithelial cells, Id-3 may contribute to the immortalization of epithelial cells.

Presented at the Annual meeting of AACR, 2002: abstract#: 2501

Id-3 is a potential mediator of progesterone receptor dependent proliferation and apoptosis in mammary glands of PR-A transgenic mice

Y. -C. Chou, N. Uehara and G. Shyamala, Division of Life Sciences, Lawrence Berkeley National Laboratory, University of California, Berkeley, California

We have shown previously that transgenic mouse carrying an imbalance in the native ratio A: B isoforms of progesterone receptor (PR) have abnormal mammary phenotypes. In particular, in mice carrying additional A form (PR-A transgenics), mammary glands have excessive ductal growth, loss of basement membrane (BM) components and cell-cell adhesion. The present studies were undertaken to examine the potential pathways responsible for the abnormal mammary phenotype of PR-A transgenics. Analyses for cell proliferation as examined by immunocytochemical analyses, using two parameters (PCNA and BrdU), revealed an increase in the glands of PR-A transgenics. More importantly, the increase was seen only in the morphogenetically disturbed epithelium. There was also an increase in cyclin D1 expression in these lesions. Mammary glands of PR-A transgenics were also resistant to apoptosis during post-lactational involution such that regression was incomplete even at five weeks after pup removal. The emergence of the abnormal mammary phenotype i.e. excessive ductal growth, loss of BM components etc. was dependent on ovarian steroids such that it was not evident in ovariectomized mice but once again became apparent with estrogen and progesterone treatment. Analyses for gene expression profiles revealed several changes in the mammary glands of PR-A transgenics and among these was Id-3. Id-3 was over-expressed in mammary epithelium of PR-A transgenics but was abolished upon ovariectomy or when treated with RU 486. Over-expression of Id-3 in PR-A transgenics did not appear to be simply tied to the hyperproliferation of epithelial cells, since this does not occur in the glands of early pregnant wildtype mice, when there is a massive increase in epithelial cell proliferation. There is extensive documentation that Id proteins promote cell proliferation and negatively regulate differentiation. Furthermore, over-expression of Id-3 is tolerated only by immortal/neoplastic cells. Taken together, these observations lead us to propose that mammary epithelial cells of PR-A transgenics are immortal and Id-3 is involved in the immortalization of these cells (supported by NIH grant CA66541 to G.S.).

Presented at the Annual meeting of The Endocrine Society: 2002;Absract #: P1-433