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Breast cancer is one of the leading causes of cancer deaths of women in the United States. Fortunately, this disease is no longer a "black box" that can only be studied empirically. Recent advances in understanding of normal mammary development and carcinogenic processes have identified a number of specific genes and processes that are dysregulated in breast cancer. This means that research on breast cancer has finally advanced to the stage where a concentrated effort in translational research will yield great strides in detection, diagnosis, and treatment. The Molecular Medicine graduate training program at Yale was recently developed to address these issues. This program was developed to offer an interdisciplinary course of study that will foster an integrated view of disease, built upon a rigorous foundation of basic sciences. The emphasis on disease mechanisms and translational research is unique to Molecular Medicine, and distinguishes it from other pre-doctoral programs at Yale. The Predoctoral Training Program in Breast Cancer Research will recruit individuals interested in careers in breast cancer research to the Molecular Medicine Program, provide specialist training in breast cancer-specific areas, and integrate their training experience with scientists and clinicians investigating breast cancer at Yale.

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INTRODUCTION

The past decade has witnessed a revolution in the power of biologists to investigate fundamental mechanisms underlying disease. This change has resulted from major advances in biological research, coupled with the extraordinary power of modern molecular genetics for identification of gene mutations in disease. The result is that investigation of many human diseases has gone beyond the descriptive level to the root causes. This new knowledge means that the tools of genetics, immunology, cell biology, molecular biology, and other disciplines can now be combined to investigate disease pathogenesis, and to apply these findings to issues of diagnosis and treatment. The Molecular Medicine graduate training program at Yale was recently developed to address these issues. This program was developed to offer an interdisciplinary course of study that will foster an integrated view of disease, built upon a rigorous foundation of basic sciences. The emphasis on disease mechanisms and translational research is unique to Molecular Medicine, and distinguishes it from other pre-doctoral programs at Yale. The Predoctoral Training Program in Breast Cancer Research will recruit individuals interested in careers in breast cancer research to the Molecular Medicine Program, provide specialist training in breast cancer-specific areas, and integrate their training experience with basic scientists and clinicians investigating breast cancer at Yale.

BODY

We have now completed the fourth year of this new training program. The program is in no-cost extension to accommodate the difference between the grant year (August to July) and the academic year (September to August). Table 1 lists the students funded during this cycle and previous years.

Recruitment. There was no new recruitment of students for this year, since, as originally planned, all funds were applied to support of ongoing students. At Yale, principal investigators cover tuition and training costs for fourth year graduate students and beyond. Of students funded by this training grant, only Alessandra Giodini (year 2), Seda Eminaga (year 3) and Leigh-Ann Higa (year 3) were funded by the grant for the academic year 2002-2003 covered in most of this report period. Remaining students are now being covered by their dissertation advisers.

	1999-2000	2000-2001	2001-2002	2002-2003	thesis adviser	Dept.
students entering 1999						
Jessica Hawes	X	X	X		**Crews/ Schlessinger/ Piccioto**	**Pharm**
Soo-Jung Lee	X	X	X		**Stern**	**Path**
Julie Wu	X	X	X		**Bennett**	**Pharm**
students entering 2000						
Seda Eminaga		X	X	X	**Bennett**	**Pharm**
Leigh-Ann Higa		X	X	X	**Zhang**	**Genetics**
Kristen Massimine*		X				**CellBio**
Alexander Urban*		X				**MCDB**
students entering 2001						
Alessandra Giodini			X	X	**Schlessinger**	**Pharm**

*now funded by other training programs at Yale

Table 1. Summary of trainees. "X" indicates that student was funded by this training program during the designated academic year.

Training. The first year in graduate school consists of course work and a series of research rotations. All incoming students were oriented along with other students in the Pharmacological Sciences and Molecular Medicine Track, and assigned to trainers and Track Directors William Sessa and David Stern as advisors. The advisors met with the students to jointly plan out a curriculum for

the first year. In year 1, this consists of course work and three laboratory rotations. The rotations serve to train individuals in design, execution, and interpretation of laboratory research projects, to expose the trainees to a variety of research experiences, and to enable trainees to identify compatible dissertation advisors. Students are required to choose a dissertation advisor the end of the first year.

Class	**Students**	**Rotations and Dissertation Advisors (underlined) **= BCRTP trainer**
entered Fall 2001	Alessandra Giodini	Ira Mellman, S. Strittmatter, Joseph Schlessinger
entered Fall 2000	Seda Eminaga Leigh-Ann Higa Kristen Massimine* Alexander Urban*	**Stern, **Rimm, **Bennett **Perkins, Bordey, Shlomchik, **Zhang Lolis, Lifton, **DiMaio Strittmatter, **Lizardi, Rakic,
entered Fall 1999	Jessica Hawes Soo-Jung Lee Julie Wu	(information provided in previous annual report)

Table 2. Students and rotations, 2000-2001.
*No longer funded by training program.
****BCRTP trainer**

Course work. As discussed in the proposal, the purpose of coursework is to ensure that students have a strong basic science foundation that complements undergraduate coursework, and to provide students with advanced and specialty knowledge. This process continued in year 2, with inclusion of breast-cancer-specific training. Classes taken by the students are described in **Table 3**, and include "foundation" courses such as cell biology and genetics, and more specialized coursework in cancer and disease mechanisms.

courses taken in year 1 or year 2	Giodini	Hawes	Lee	Wu	Eminaga	Higa	Massimine	Urban
Fall term.								
Advanced Biology Lab								•
Cell Biology 602a Molecular Cell Biology	•	•	•	•	•			
Genetics 625a Basic Concepts of Genetic Analysis		•	•				•	•
Pathology 680a seminar Topics in Molecular Medicine: Matrix Biology	•	•	•	•	•	•	•	•
Pharmacology I:Maintaining and restoring homeostasis				•		•		
Pathology 640a From Molecular Biology to Molecular Medicine								
Signal Transduction Seminar						•		
Apoptosis Seminar						•		
Physiological Systems I					•		•	
Medical Physiology								•
MBandB 752a Genomics/Bioinformatics								
Spring term.								
Pathology 650b Cellular and Molecular Biology of Cancer	•	•	•	•				
Biotechnology							•	
Human Molecular Genetics	•							
Pathology 660b Biology and Therapy of Breast Cancer			•	•	•	•		
Medical Physiology								•
Pathology 690b Mechanisms of Disease	•	•						
Pharmacology II: Interfering selectively	•	•	•	•	•	•	•	
Pharm 518b Current Topics in Cancer and Viral Therapy					•		•	
Pharm 502b seminar	•	•	•	•	•	•	•	•

Table 3. Coursework by trainees in years 1 and 2, 2000-2002.

Trainees and their projects.e

Trainees were recruited over a period of three consecutive years from inception of the training grant. Because of the flexibility inherent to the Yale BBS program, two of the eight students funded during their first year eventually opted for labs outside of the training program. Dissertation projects for remaining students are summarized in Table 4, and are described in detail below. Note that the focus of some of these projects has shifted since the last annual report.

Dissertation Projects

student	adviser	dissertation project
Seda Eminaga*	Bennett	Substrates for SHP-2 SH2-containing protein-tyrosine phosphatase Breast Cancer Relevance: component of central signaling pathway for breast cancer oncogenes
Alessandra Giodini	Schlessinger	FGF-receptor- Gprotein coupled receptor crosstalk through FRS2 Breast Cancer Relevance: modulation of important breast cancer oncogene signaling system
Jessica Hawes*	Crews/ Schlessinger/ Piccioto	Differential signaling by adapter proteins FRS1 and FRS2 Breast Cancer Relevance: FGFR-activated docking proteins mediate important breast CA oncogene pathway
Leigh-Ann Higa*	Zhang	Regulation of DNA replication through Geminin and Cdt1 Breast Cancer Relevance: Cell cycle regulation and checkpoint responses; treatment implications
Soo-Jung Lee*	Stern	DNA damage checkpoint Signaling in Mec1⇒Rad9⇒Rad53 pathway in budding yeast Breast Cancer Relevance: homologous to mammalian pathway Atm or Atr ⇒ ⇒ Chk2 ⇒ p53 including breast cancer tumor suppressor genes; treatment implications
Julie Wu*	Bennett	EGFR-dependent regulation of MAPKinase Phosphatase through Ca++. MAPK P'tase in stress responses. Breast Cancer Relevance: EGFR important breast CA oncogene and therapeutic target

Table 4. Summary of Dissertation Projects.
*Research publications in preparation or published during the training period

Students in year 4, 2002-2003. (funded by their dissertation advisers)

Soo-Jung Lee. Ms. Lee continues her work in the laboratory of the program director, Dr. Stern. The major components of DNA checkpoint pathways are conserved between budding yeast and humans. The Stern lab is investigating DNA checkpoint pathways connecting DNA damage to activation of the yeast ortholog of human Atm (yeast Mec1), which in turn activates human Chk2 (yeast Rad53). Ms. Lee is presently working on in vitro activation of Rad53 activation. by the Atm homolog Mec1. Thus, studying the mechanism of RAD53 activation by Mec1/Tel1-Rad9 in yeast will provide important clues to understanding well conserved DNA damage checkpoint signaling pathway. Her work this year included analysis of regulation of Rad53 by phosphorylation, and by binding of proteins to its FHA domains. This work resulted in two publications in 2003. Ongoing work is to reconstitute interactions of Rad9, Rad53, and Mec1 in vitro.

Schwartz, M.F., Lee, S.J., Duong, J.K., Eminaga, S., and D.F. Stern. 2003. FHA domain-mediated DNA checkpoint regulation of Rad53. Cell Cycle 2:384-396.

Lee, S.-J., Schwartz, M.F., Duong, J.K, and D.F. Stern. 2003. Rad53 Phosphorylation Site Clusters Are Important for Rad53 Regulation and Signaling. Mol.Cell.Biol 23:6300-6314.

Breast cancer relevance. This work is directly relevant to breast cancer, since it is now clear that Chk2 is an intermediary linking DNA checkpoint pathways from candidate breast cancer tumor suppressor Atm to breast cancer tumor suppressor p53; since Chk2 phosphorylates and modulates Brca1 function, and since Chk2 mutations are found in variant p53+ forms of Li-Fraumeni syndrome, which predisposes to breast cancer and other cancers.

Julie Wu. Ms. Wu is working in the laboratory of trainer Anton Bennett. Mitogen activated protein kinase (MAP) phosphatase 1 (MKP1) is a dual specificity tyrosine/threonine phosphatase that is highly regulated by growth regulators and stress. It dephosphorylates MAPK family members. MKP1 regulates the activities of p38 (Stress activated protein kinase) and ERKs. Attenuation of MAPK activity after activation is a tightly regulated process.

MKP-1 is protein dual specific protein phosphatases that regulates cellular proliferation and apoptosis through dephosphorylation and inactivation the MAPK family members, ERK, JNK and p38. MKP-1 is an immediate early gene that is regulated by growth factors and stress. It has been shown that MKP-1 expression is increased in hepatocytes during liver regeneration and osmotic stress. The role of MKP-1 in hepatocytes has not been examined. Ms. Wu's project has two components. (1) She isdetermining how EGF immobilization of cytoplasmic and nuclear calcium regulates MKP-1 gene expression and ERK activation. In hepatocytes, activation of the EGFR increases calcium levels in the cytoplasm as well as in the nucleus. Overexpression of a calcium chelating protein parvalbumin fused to a nuclear exclusion or nuclear localization sequence is used to inhibit EGF mobilization of calcium in the cytoplasm or nucleus respectively. ERK activity and the transactivation activity of its substrate, Elk-1 in response to EGF stimulation are measured. MKP-1 promoter activity is measured as a read out for MKP-1 expression. (2) The role of MKP-1 in vivo has not been examined. MKP-1 knockout mice have been generated, and no apparent phenotype was observed. Over the last year, She has been increasing the size of the MKP-1 knockout mice colony. Preliminary biochemical analysis of primary hepatocytes isolated from wild type or MKP-1 knockout mice has been performed.
Breast cancer relevance. MAPKs are major regulators of cell growth and apoptosis. Oncogenes such as Ras and ErbB2 function in part through activation of MAPKs. Regulation of MAPK attenuation may be as important as regulation of activation. Inability to attenuate the activity of activated proteins results in abnormal biological processes. Inability to attenuate a p38 MAPK activity during stress may uncouple the cell's ability to respond to stress and repair induced damage. This may result in gene mutations, and/or unregulated growth, two hallmarks of cancer.

Pusl T, **Wu JJ**, Zimmerman TL, Zhang L, Ehrlich BE, Berchtold MW, Hoek JB, Karpen SJ, Nathanson MH, Bennett AM. Epidermal growth factor-mediated activation of the ETS domain transcription factor Elk-1 requires nuclear calcium.
J Biol Chem. 2002 277(30):27517-27.

Fornaro M, Steger CA, Bennett AM, **Wu JJ**, Languino LR. Differential role of beta(1C) and beta(1A) integrin cytoplasmic variants in modulating focal adhesion kinase, protein kinase B/AKT, and Ras/Mitogen-activated protein kinase pathways.
Mol Biol Cell. 2000 Jul;11(7):2235-49.

Jessica Hawes. Ms. Hawes was working in Joseph Schlessinger's laboratory to investigate FRS2-dependent and independent fibroblast growth factor signaling. Mid-year, she switched to Marina Picciotto's laboratory, where she is now working on Galaninergic Signaling and Drug Addiction.

Galanin receptors 1 and 2 have been shown to be upregulated in several brain and small lung carcinomas. However, the current project focuses on the role of galanergic signaling during drug

addiciton. The neuropeptide galanin has been shown to attenuate opiate reinforcement in mouse models and preliminary data suggests that the small molecule galanin agonist galnon can attenuate opiate withdrawal in vivo. The long term objective of my project is to elucidate the molecular mechanisms through which galaninergic signaling attenuates opiate reinforcement and withdrawal.

Breast cancer relevance. Fibroblast growth factors are important growth regulators in normal and malignant mammary tissue. FRS2 is a major mediator of FGF responses, and is relatively specific to this receptor system. Learning about the FRS2-regulated pathways will help clarify the mechanisms of FGF-regulated mammary proliferation, and may lead to therapeutics that target this pathways. The new work on galanin receptors may be relevant to pain responses in the cancers where the receptors are overexpressed.

Zachariou V, Brunzell DH, **Hawes J**, Stedman DR, Bartfai T, Steiner RA, Wynick D, Langel U, Picciotto MR. The neuropeptide galanin modulates behavioral and neurochemical signs of opiate withdrawal. *Proc Natl Acad Sci U S A*, 2003 Jul 22;100(15):9028-33.

Students in year 3, 2002-2003 who remained in the training program. (dissertation work)

Seda Eminaga. Ms. Eminaga is identifying substrates for protein tyrosine phosphatase SHP-2. SHP2 is a widely expressed protein that has been shown to be a positive transducer of signaling pathways such as MAPK, PDGF, EGF, and Insulin pathways. In addition, there are reports that suggest that SHP-2 is involved in cell migration, adhesion and angiogenesis. SHP-2 has also been shown to be downstream of IL-6 which is known to support cell growth and prevent apoptosis.

Data from the Bennett lab shows that SHP-2 is required for positive signaling during C2C12 myogenesis, as well as during IGF-1 receptor signaling. However, the true physiological substrates of SHP-2 remain unidentified. The pathways that SHP-2 is involved with are likely to have important therapeutic implications in cancer thus, SHP-2 might be a potential target for drug development. Ms. Eminaga's focus is to identify potential substrate(s) of SHP-2 and therefore, better understand how SHP-2 is involved in the regulation of normal cellular pathways and ultimately, its role in cancer.

Evidence suggests that SHP-2 acts upstream of the small G protein Rho GTPase. In addition, tyrosine phosphorylation of p190RhoGAP-B, a negative regulator of Rho, decreases during C2C12 myogenesis. Interestingly, SHP-2 protein expression and activity levels increase duing C2C12 myogenesis. These observations suggest that p190RhoGAP-B might be a potential substrate of SHP-2. Currently, I am determining whether p190-B is a true physiological substrate of SHP-2, and whether dephosphorylation of p190-B by SHP-2 is a major mechanism by which SHP-2 exerts its effect during C2C12 myogenesis.

In addition, recent evidence suggests that p190-B regulates mammary ductal morphogenesis. p190-B heterozygous mice have been shown to exhibit less ductal outgrowth when compared to wild type mice. Based on the observations during C2C12 myogenesis, it will be interesting to determine whether SHP-2 regulates ductal morphogenesis via regulation of p190-B tyrosine phosphorylation.

Breast cancer relevance. SHP2 is activated by many growth activating receptor kinases, including EGFR, IGF1R, and ErbB2. These studies will clarify how SHP-2 functions in growth regulation. Other processes regulated by SHP-2, migration, adhesion, and angiogenesis, are important in invasion and metastasis. The connection of p190B with mammary morphogenesis suggests a direct link of this pathway with mammary carcinoma. Understanding how these pathways work have important therapeutic implications in cancer and, as a positive growth regulator, SHP-2 is a potential target for drug development.

Schwartz, M.F., Lee, S.J., Duong, J.K., **Eminaga, S.,** and D.F. Stern. 2003. FHA domain-mediated DNA checkpoint regulation of Rad53. Cell Cycle 2:384-396.

Leigh-Ann Higa. Ms. Higa is investigating the link between DNA damage, repair, and replication. Her research focuses on the regulation of Cdt1, a DNA replication initiation factor, after DNA damage. Cdt1 is a critical component of the pre-replication complex (pre-RC), a multiprotein complex assembled on replication origins during G1. Assembly and activation of the pre-RC is tightly controlled by the cell cycle to ensure complete and timely duplication of the genome.

Utilizing both mammalian and Drosophila cultured cells, the lab has found that Cdt1 is rapidly proteolyzed after ionizing radiation (IR). Cdt1 protein levels decrease within minutes of IR, and occurs via a ATM/CHK2 independent pathway. Ubiquitin mediated proteolysis represents a major regulatory mechanism in the cell cycle, and the specificity towards proteolytic targets is determined by a class of enzymes known as E3 ubiqutin ligases. The prototypical E3 ubiquitin ligase is the SCF (Skp2, Cdc53/cullin, F box protein) complex. Skp2 serves as an adaptor protein that brings together the F box protein (which directly interacts with substrate) and the cullin core (which interacts with the ubiquitin conjugating machinery). She has identified a cullin 4-containing E3 ligase as responsible for Cdt1 degradation: loss of cullin 4 by RNA interference prevents Cdt1 proteolysis after IR, and cullin 4 complexes can ubiquitinate Cdt1 in vitro. In vivo, Cdt1 proteolysis in G1 delays entry into S phase, suggesting that Cdt1 is a critical target of a DNA damage checkpoint for DNA replication. Future research will involve identification of the F box protein for Cdt1 degradation, and analysis of the signaling pathway downstream of Cdt1 degradation.

Breast cancer relevance. Understanding this pathway is essential for understanding genome destabilization, an important component of carcinogenesis. It may also aid in better using existing genotoxic anti-cancer drugs, since these genes are an important component of the protective response to DNA damage.

a manuscript on the Cdt1 work has been submitted for publication

Mihaylov IS, Kondo T, Jones L, Ryzhikov S, Tanaka J, Zheng J, **Higa LA**, Minamino N, Cooley L, Zhang H. Control of DNA replication and chromosome ploidy by geminin and cyclin A. Mol Cell Biol. 2002 Mar;22(6):1868-80.

Students in year 2, 2002-2003.

Alessandra Giodini

Ms. Giodini's project in Yossi Schlessinger's laboratory is the characterization of the cross-talk between two families of receptors: Receptor Tyrosine Kinases (RTKs) and G-Protein Coupled Receptors (GPCRs). In paricular, this cross-talk seems to be mediated by the docking protein FRS2 alpha.

Lysophosphatidic acid (LPA), the simplest of all phospholipids, exhibits pleiomorphic functions in multiple cell lineages. The effects of LPA appear to be mediated by binding of LPA to specific members of the endothelial differentiation gene (Edg) family of G protein-coupled receptors (GPCR). The specific biochemical events initiated by the different Edg receptors, as well as the biological outcomes of activation of the individual receptors, are only beginning to be determined. LPA levels are consistently elevated in the plasma and ascites of ovarian cancer patients, but not in most other epithelial tumors, with the exception of cervix and endometrium, suggesting that LPA may be of particular importance in the pathophysiology of ovarian cancer. In support of this concept, ovarian cancer cells constitutively and inducibly produce high levels of LPA and demonstrate markedly different responses to LPA than normal ovarian surface epithelium. Thus, increased levels of LPA, altered receptor expression and altered responses to LPA may contribute to the initiation, progression or outcome of ovarian cancer.

Breast Cancer Relevance. RTKs including ErbBs and FGFRs are important in breast cancer and are therapeutic targets. Work on LPA modulation of these receptors will yield insights into potential mechanisms for cross-regulation, and perhaps direct regulation of these cancers by LPA.

the following publications from Ms. Giodini for work accomplished

In year 2 these students will complete coursework, including breast cancer training, qualifying exams, and will begin to lay the foundation for the dissertation. Although the students have dissertation advisors, the dissertation project is not formalized until the prospectus exam, which must be completed by the end of year 3. A brief description of research directions of the five students is now provided, with the caveat that it may be some time before the projects fully evolve.

Key Research Accomplishments for 2002-2003

- Continued funding/training of four graduate students in years 2 and 3 of graduate school, and monitoring of students in year 5.
- Continued progress of (nonfunded) students in year 4 towards careers in cancer research
- Six publications resulting from work conducted by trainees, with one more submitted for publication.

Reportable outcomes. Trainees are marked in bold.

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Mihaylov IS, Kondo T, Jones L, Ryzhikov S, Tanaka J, Zheng J, **Higa LA**, Minamino N, Cooley L, Zhang H. Control of DNA replication and chromosome ploidy by geminin and cyclin A. Mol Cell Biol. 2002 Mar;22(6):1868-80.