NEW YORK STATE HEALTH RESEARCH SCIENCE BOARD

BIENNIAL REPORT

January 1, 2007 to December 31, 2008

December 31, 2008

State of New York
Department of Health

Health Research Science Board
Membership Roster
January 1, 2007 - December 31, 2008

Santo M. DiFino, M.D., Chair
Hematology-Oncology Associates of Central New York, P.C.
Syracuse, NY

Christine B. Ambrosone, Ph.D. [1]
Roswell Park Cancer Institute
Buffalo, NY

Geraldine Barish [3]
1 in 9, Long Island Breast Cancer Coalition
Baldwin, NY

Beverly Canin [1, 2]
Survivor, Hudson Valley Region

Heather C. Dantzker, Ph.D. [1, 3]
Cornell University
Ithaca, NY

Gail Frankel [1, 4]
Survivor, Long Island Region

Alexander P. Gross, M.S. [1, 5]
Man-to-Man Awareness and Support Group
Syracuse, NY

M. Suzanne Hicks, M.S.W. [1, 4]
Survivor, Northern NY Region

Russell Hilf, Ph.D. [1]
University of Rochester School of Medicine and Dentistry
Rochester, NY

Carl Johnson, M.S. [3]
New York State Department of Environmental Conservation, Commissioner's Designee
Albany, NY

Laurence S. Kaminsky, Ph.D. [1, 3]
Wadsworth Center
New York State Department of Health
Commissioner's Designee
Albany, NY

Philip J. Landrigan, M.D., M.Sc. [6]
Mount Sinai School of Medicine
New York, NY

Thomas J. Lester, M.D. [1]
Katonah Medical Group, P.C.
Katonah, NY

Gary Morrow, Ph.D. [1, 4]
University of Rochester
Rochester, NY

Alexander Yu. Nikitin, M.D., Ph.D. [3, 6]
Cornell University
Ithaca, NY

Arun Puranik, M.D. [1]
Image Guided Radiation Therapy
Latham, NY

Robert Riter [1, 2]
Survivor, Central NY Region

Neeta Shah, M.D. [1, 4]
North Shore Long Island Jewish Health Systems
New Hyde Park, NY

Elinor J. Spring-Mills, Ph.D. [1]
SUNY Upstate Medical University
Syracuse, NY

Jean Wactawski-Wende, Ph.D. [1]
University of Buffalo
Buffalo, NY

Val Washington, Esq. [1, 3]
New York State Department of Environmental Conservation
Commissioner's Designee
Albany, NY

Marc Wilkenfeld, M.D. [1]
Columbia University Medical Center
New York, NY

[1] Current Board member
[2] Non-voting member
[3] *Ex-officio* non-voting member
[4] Became voting member during 2008
[5] Past *ex-officio* non-voting member; appointed as voting member in 2008
[6] Resigned during 2008

Department of Health Staff

Wadsworth Center
Extramural Grants Administration

Bonnie Jo Brautigam
Director

Teresa Ascienzo
Associate Accountant

Lani Rafferty
Health Program Administrator

Center for Environmental Health

Nancy Kim, Ph.D.
Senior Executive

Carole Ju, M.S.
Research Scientist
Bureau of Environmental and Occupational Epidemiology

Division of Legal Affairs

Diana Yang, Esq.
Bureau of House Counsel

Department of Environmental Conservation Staff

Valerie Washington, Esq.
Deputy Commissioner
Remediation and Materials Management

Margaret O'Neil
Chief, Pesticide Reporting and Certification Section
Bureau of Pesticides Management

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Executive Summary

HEALTH RESEARCH SCIENCE BOARD BIENNIAL REPORT

2007-2008

The Health Research Science Board (HRSB) of the New York State Department of Health (DOH) was established pursuant to Chapter 279 of the Laws of 1996 (amended by Chapter 219 of the Laws of 1997 and Chapter 32 of the Laws of 2008). The legislation is codified in Title 1-B, Article 24 (§ 2410-2413) of the New York State Public Health Law (PHL). Chapter 279 also established the Breast Cancer Research and Education Fund, to be financed through voluntary contributions from a check-off mechanism on the New York State Income Tax form (§ 97-yy of the State Finance Law). New York State subsequently began matching those donations pursuant to Chapter 550 of the Laws of 2000.

Chapter 279 also established a Pesticide Sales and Use Database, maintained by the New York State Department of Environmental Conservation (DEC) in conjunction with Cornell University, pursuant to Environmental Conservation Law (ECL) § 33-1201 through § 33-1207. The database contains mandated reports on pesticide applications submitted to DEC by all commercial applicators. Sales of pesticides for use in agricultural crop production are reported to the database by entities that sell, or offer for sale, restricted-use pesticides to private applicators. Most of the information in the database is available to the public; however, the Board is responsible for considering and approving the release of confidential pesticide information for specific health-related research projects.

The Board is grateful to the many New York State residents who have contributed so generously to the Breast Cancer Research and Education Fund, and to the Governor and Legislature for the statute that provides for State matching of income tax donations.

Among the Board and its program's highlights of accomplishments in 2007 and 2008 were:

- More than $1.10 million in funds was contributed via the income tax check-off mechanism during the period covered by this biennial report. This amount is matched dollar-for-dollar from State funds. The total dollar amount of these gifts has remained fairly consistent during the past five years, despite a gradual decline in the number of tax returns with gifts.

- During 2007-2008, new legislation (Chapter 32 of the Laws of 2008) established five additional voting member seats and three non-voting member seats. Four voting members have been seated; five voting member and one non-voting member vacancies remain. One *ex-officio* member was replaced.

- The Board's Committee on Access to Pesticide Registry and Pesticide Application Information received one application from the Cornell University Department of Biological and Environmental Engineering requesting confidential Pesticide Registry Sales and Use Database information. The Board approved the request. An abstract of the ensuing research projects and contact information for the researchers involved are found in Appendix XII.

- Eighteen (18) scientific papers were published during 2007-2008 in peer-reviewed journals as the result of Board-funded projects (see Appendix IX, Publications, Presentations and Meeting Abstracts Based on Awards).

- The HRSB symposium, “Advancing Breast Cancer Research in New York State,” was held on October 26, 2007.

- Program profile brochures were developed and distributed to past and present contractors, academic research institutions, and other interested parties.

- At its October 3, 2008 meeting, the Board adopted bylaws changes to allow for future expansion and enhanced performance of its standing committees, and management of the peer-review process via a contractor.

The Board appreciates the opportunity to work for the citizens of New York State to support critical public health research and education in breast cancer, and stimulate economic development. The Board looks forward to and anticipates continued progress and success in achieving its mandates.

STATE OF NEW YORK
DEPARTMENT OF HEALTH

HEALTH RESEARCH SCIENCE BOARD

BIENNIAL REPORT

January 1, 2007 to December 31, 2008

I. INTRODUCTION

The Health Research Science Board (HRSB) of the New York State Department of Health (DOH) was established pursuant to Chapter 279 of the Laws of 1996 (amended by Chapter 219 of the Laws of 1997 and Chapter 32 of the Laws of 2008). The legislation is codified in Title 1-B, Article 24 (§ 2410-2413) of the New York State Public Health Law (PHL). Chapter 279 also established the Breast Cancer Research and Education Fund, to be financed through voluntary contributions from a check-off mechanism on the New York State Income Tax form (§ 97-yy of the State Finance Law). New York State subsequently began matching those donations pursuant to Chapter 550 of the Laws of 2000.

Chapter 279 also established a Pesticide Sales and Use Database, maintained by the New York State Department of Environmental Conservation (DEC) in conjunction with Cornell University, pursuant to Environmental Conservation Law (ECL) § 33-1201 through § 33-1207. The database contains mandated reports on pesticide applications submitted to DEC by all commercial applicators. Sales of pesticides for use in agricultural crop production are reported to the database by entities that sell, or offer for sale, restricted-use pesticides to private applicators.

The Board's primary responsibilities, as delineated in PHL § 2411(1), include:

- **Recommending awards for research and education**

  The Board is directed to solicit, receive, and review applications from various entities for grants to conduct research and education programs focusing on the causes, prevention, screening, treatment and cure of breast cancer. Such research funding is distributed through a formal Request for Applications (RFA) process and executed contracts.

- **Reviewing requests for access to pesticide-related data**

  The Board is responsible for evaluating requests for and granting access to confidential pesticide-related data collected and maintained in the Pesticide Sales and Use Database. The data include: 1) reports of pesticide applications submitted to DEC by commercial applicators and technicians; 2) reports of sales of restricted pesticides to private applicators; and 3) reports of general-use pesticide sales for use in agricultural crop production. While portions of the database are public, much of it is confidential and may only be released to those engaging in human health-related research, pursuant to the Board's approval and contingent on compliance with established criteria.

This, the Board's sixth biennial report, summarizes its 2007-2008 activities and program operations with regard to its major functions. The Board's enabling statutes are found in Appendices I-V and

the bylaws governing the Board's activities are found in Appendix VI. As required by statute, this biennial report includes:

1. the Board's recommendations on matters including, but not limited to, the types of pesticide data useful for breast, prostate or testicular cancer research; and whether private citizen use of residential pesticides should be covered in the reporting requirements;

2. a summary of research requests for pesticide data granted and denied;

3. an evaluation by the Commissioners of Health and Environmental Conservation, as well as the Board, of the basis, efficiency and scientific utility of the information derived from pesticide reporting pursuant to ECL § 33-1205 and 33-1207, and recommendations on whether such an information system should be modified or continued; and

4. a summary of comments and recommendations presented by the public at the Board's public hearings.

II. BOARD ORGANIZATION AND STAFF SUPPORT

In 2008, legislation was adopted to enlarge the Board and reconfigure its composition to include voting representation from breast cancer survivors. As a result, the HRSB structure now includes 17 voting members and six non-voting members, as follows: 12 voting doctoral-level scientists and physicians appointed by the Governor and the Legislature; three voting regional breast cancer survivors who are actively involved with a community-based, grass-roots breast cancer organization; one voting breast cancer survivor and one voting prostate or testicular cancer survivor; three non-voting *ex-officio* members representing the DOH, the DEC, and Cornell University's Institute for Comparative and Environmental Toxicology; and three non-voting regional breast cancer survivors who are actively involved with a community-based, grass-roots breast cancer organization. The Board's Chair is designated by the Governor. Member terms are three years in length, with reappointment permitted. An individual member's Board service may continue beyond the prescribed term until the member is replaced. This process is designed to ensure the stability and continuity of the Board.

DOH staff have worked closely with the advocacy and survivor communities to facilitate the membership transition. The Governor appointed two members recommended by the Senate, and also appointed two voting and one non-voting member. DOH staff provided new members with orientation materials and convened orientation conference calls to update them on recent Board business prior to their first Board meeting. The Board currently includes 12 voting members.

While the legislation does not allocate funding for support staff and administration of the Board's Program, the DOH supplies such support to the Board. The DEC maintains the Pesticide Sales and Use Database, and reports on the basis, efficiency and scientific utility of the information derived from pesticide reporting.

A. Voting Members as of December 31, 2008

SANTO M. DIFINO, M.D., Chair

Dr. DiFino is a clinician with Hematology-Oncology Associates of Central New York, P.C.; Chief of Internal Medicine, St. Joseph's Hospital Health Center; and associate clinical professor, Department of Medicine, State University of New York (SUNY) Upstate Medical Center,

Syracuse, New York (NY). He earned a B.S. degree in biology, *magna cum laude*, from Fordham University. Dr. DiFino was elected to Phi Beta Kappa and obtained his medical degree in 1974 from the New Jersey Medical School. Dr. DiFino interned and completed a residency in medicine at the SUNY Upstate Medical Center, Syracuse. He is board-certified in internal medicine, medical oncology and hematology.

Since 1992, Dr. DiFino has been a principal investigator/associate investigator with the Community Clinical Oncology Program in Syracuse; he also is a member of Cancer and Leukemia Group B. Dr. DiFino is president of the Central New York Chapter of the Leukemia Society of America and was recipient of the Leukemia Society's Man of the Half Century Award. As a result of his active involvement in community service, he was nominated as Health Citizen of the Year and is a recipient of the President's Medallion from Catholic Charities of Syracuse. Dr. DiFino is chair of the Board's Funding and Outreach Committee.

Dr. DiFino has served the Board since April 1997.

CHRISTINE B. AMBROSONE, Ph.D.

Dr. Ambrosone is professor of oncology and chair of the Department of Cancer Prevention and Control at Roswell Park Cancer Institute (RPCI) in Buffalo, NY. Prior to coming to RPCI, Dr. Ambrosone was director of the Derald H. Ruttenberg Cancer Center at Mount Sinai School of Medicine in New York City.

She serves as senior editor for the journal *Cancer Research*, and is on the Board of Scientific Advisors to the Director of the National Cancer Institute (NCI). She has been a peer reviewer for two dozen, mostly cancer, journals, including *Breast Cancer Research*, and *Breast Cancer Research and Treatment*. Dr. Ambrosone also has extensive experience as a grant review committee member in breast, ovarian and prostate cancer competitions, and has served on the Integration Panel for the United States (U.S.) Department of Defense Breast Cancer Research Program. She has been principal investigator or co-principal investigator of 15 funded studies, many of them supported by the National Institutes of Health (NIH). She is the author or co-author of more than 100 published articles and book chapters, and is a sought-after lecturer. Dr. Ambrosone graduated with a bachelor's degree from SUNY at Buffalo, *summa cum laude*, and was elected to Phi Beta Kappa. She received her master's and doctor of philosophy degrees from RPCI and SUNY at Buffalo.

Dr. Ambrosone has served the Board since July 2004.

GAIL FRANKEL

Gail Frankel was diagnosed with breast cancer in 1993, and underwent a lumpectomy and radiation therapy. In 1995, she joined the Adelphi NY Statewide Breast Cancer Hotline and Support Program and became a telephone volunteer, outreach coordinator and speaker/activist about breast cancer. As part of her speaking engagements, she has appeared at the Adelphi Celebration of Survivorship, co-chaired two Era of Hope symposia, testified before U.S. Senate and House subcommittees, co-chaired a workshop on the Long Island Study Project at the National Breast Cancer Coalition (NBCC) Advocate Training Conference, and appeared in several television spots concerning breast cancer-related news. As the NBCC's Field Coordinator for Long Island, she lobbies Congress on breast cancer issues and serves on U.S. Congressional Representative Tim Bishop's Breast Cancer Advisory Board. She is a graduate

of the Project Leadership Education Advocacy Development (LEAD) institute, the NBCC Fund's premier science training course for activists.

In 2001, Ms. Frankel became a consumer reviewer on the Board's panel, a position she also has held on the U.S. Department of Defense Breast Cancer Research Program since 2006. For the past six years, she has been a community member of Stony Brook University Medical Center's Institutional Review Board.

Ms. Frankel began serving the Board in July 2008.

ALEXANDER P. GROSS, M.S.

Mr. Gross is a prostate cancer survivor who underwent radiation therapy in 1993 and subsequently, combined hormone blockage therapy. He is an active member of Man-to-Man Awareness and Support Group in Syracuse, NY, and has served as editor of its newsletter. He also is a member of the DOH Prostate and Testicular Cancer Detection and Education Advisory Council.

Mr. Gross is a retired engineering project manager in the former Aerospace Division of the General Electric Company. He received a B. E. degree in mechanical engineering from Stevens Institute of Technology and an M.S. degree from Syracuse University. He was a licensed New York State (NYS) professional engineer.

Mr. Gross has served the Board as an *ex-officio* non-voting prostate cancer survivor since March 2001, and was appointed as a voting member in July 2008.

M. SUZANNE HICKS, M.S.W.

M. Suzanne Hicks is a seven-year melanoma survivor and a five-year breast cancer survivor. Ms. Hicks holds a B.S. in English education from the University of Tulsa, and an M.S.W. degree from the SUNY at Albany. She is a clinical assistant professor of psychiatry at Albany Medical College and closed a 30-year psychotherapy practice in Albany, NY in 2005. Locally, she is a member of the Capital Region Action Against Breast Cancer!, a community-based education and advocacy group. At the national level, she is very active in the NBCC, where she serves on the "KnowBreastCancer.org" Advisory Committee. Ms. Hicks has participated in the NBCC Fund's Project LEAD (Leadership, Education and Advocacy Development), an intensive course for advocates on the basic science of breast cancer and advocacy issues, and was a speaker at the NBCC Annual Advocacy Conference in 2008.

She has started a local breast cancer peer study group, and spends much of her time as a breast cancer advocate and as an artist with a studio in Albany, NY.

Ms. Hicks began serving the Board in July 2008.

RUSSELL HILF, Ph.D.

Dr. Hilf is professor of biochemistry and oncology at the University of Rochester School of Medicine and Dentistry. He earned a B.S. in chemistry from the City College of New York in 1952, and an M.S. and Ph.D. in biochemistry from Rutgers University. After serving in the U.S.

Army and briefly at the Q.M. Food & Container Institute, he held the position of head of cancer endocrinology at the Squibb Institute for Medical Research for 11 years, prior to joining the faculty at the University of Rochester School of Medicine and Dentistry in 1969.

Dr. Hilf's primary research interests lie in the field of hormone action, with emphasis on estrogen and anti-estrogen mechanisms, and on insulin and IGF-1, as they pertain to breast cancer. A second area of research deals with photodynamic therapy of neoplasms. Dr. Hilf has published more than 200 peer-reviewed papers in professional journals and written 40 invited book chapters. He is a member of the American Association for Cancer Research, American Society for Biochemistry and Molecular Biology, The Endocrine Society, and the American Society for Photobiology. He has served as associate editor at *Cancer Research* for 20 years, and has been on the advisory board of *Biochemical Pharmacology* and the editorial boards of *Oncology Research* and *Cancer Biochemistry Biophysics*. He was elected a fellow by American Association for the Advancement of Science in 1966, received the University of Rochester Alumni Award for Graduate Education in 1992, was a Wellcome Visiting Professor in 1994, and was presented with the Davey Memorial Cancer Research Award by the University of Rochester Cancer Center in 1998.

Dr. Hilf has been a member of: the National Cancer Institute (NCI) Breast Cancer Task Force; the Veterans' Administration Merit Review Board on Oncology; the NCI Cancer Education Committee; and the American Cancer Society's Biochemistry and Chemical Carcinogenesis Committee as chair of its Biochemistry and Endocrinology Committee. He has served three cycles on the U.S. Army Breast Cancer Review Program and two terms on the NIH Reproductive Endocrinology Study Section, the last two years as chairman. He has completed two terms on the External Scientific Advisory Board for the University of Wisconsin Comprehensive Cancer Center. He also is a member of a scientific review panel for The American Institute for Cancer Research, and a reviewer of grant applications for the New Jersey Cancer Commission.

Dr. Hilf has served the Board since April 1997.

DONNA JURASITS

Ms. Jurasits has been a breast cancer survivor since 1997. She holds a B.S. in health and human services from SUNY's Empire State College, and has 20 years of social work and case management experience. She is executive director of the Babylon Breast Cancer Coalition, Inc., a community-based education and advocacy group, and previously served as the Coalition's vice president from 2003 to 2007. She was program director of the Central Islip Civic Council, Inc., a non-profit, community-based agency dedicated to improving the quality of life for all residents of Central Islip, from 1990 to 2007. She has been a member of the Suffolk County Cancer Task Force since 2006.

Ms. Jurasits was named the Town of Babylon Volunteer of the Year in 2000, and was recognized as one of *Newsday's* Everyday Heroes in 2002. She volunteers at both the American Cancer Society and the Good Shepherd Hospice.

Ms. Jurasits began serving the Board in October 2008.

THOMAS J. LESTER, M.D.

Dr. Lester practices internal medicine, hematology and oncology in Katonah, NY. He graduated with a B.S. degree, *summa cum laude*, from Washington and Jefferson College in 1975, where he was elected to Phi Beta Kappa; and from Rutgers Medical School, with honors, in 1979. Dr. Lester received his medical training in internal medicine and hematology at Mt. Sinai Hospital and in medical oncology at Memorial Sloan-Kettering Cancer Center, both in New York City.

Dr. Lester has been in private practice at the Katonah Medical Group, P.C., since 1986, where he serves on the executive committee; and has attending staff privileges at Northern Westchester Hospital Center in Mt. Kisco, NY, where he is a member of the Board of Trustees.

Dr. Lester has served the Board since July 1997.

GARY R. MORROW, Ph.D., M.S.

Dr. Morrow is professor of radiation oncology and professor of psychiatry at the University of Rochester School of Medicine and Dentistry. He also serves as an Associate Director for Cancer Control at the James P. Wilmot Cancer Center, University of Rochester. He holds undergraduate degrees in mechanical engineering and in English from the University of Notre Dame. Following college, he served in the U.S. Navy Nuclear Power Program for four years and completed patrols on the U.S.S. James K. Polk. He received a M.S. in psychology and a Ph.D. in clinical psychology from the University of Rhode Island, prior to joining the University of Rochester, where he completed an internship in clinical psychology and a two-year postdoctoral training fellowship in psychosomatic medicine. He also has earned an M.S. in medical statistics from the University of Rochester.

Since 1982, Dr. Morrow has authored more than 200 peer-reviewed publications in cancer control and been awarded continuous funding for his research in supportive cancer care and management of cancer and cancer treatment-related side effects. At present, he directs a research base for the NCI's Community Clinical Oncology Program that serves 25 affiliated collaborating institutions throughout the country and has referred more than 600 patients a year to Phase III cancer control clinical trials. His ongoing research expands upon investigations into better understanding and management of cancer-induced nausea and cancer-related fatigue.

Dr. Morrow has chaired more than two dozen permanent and *ad hoc* grant-funded review committees for the American Cancer Society, NIH, NCI and the U.S. Department of Defense. He has served on the American Cancer Society Executive Council, as well as the Advisory Council to the National Institute of Nursing Research.

Dr. Morrow began serving the Board in December 2008.

ARUN PURANIK, M.D.

Dr. Puranik is director of Image Guided Radiation Therapy in Latham, NY. He obtained a B.S. degree from Holkar Science College, Indore, India; and an M.B.B.S. and a medical degree in radiotherapy from M.G.M. Medical College, also in Indore. Dr. Puranik's postgraduate training included an internship in general medicine at M.R. Hospital, followed by appointment as resident and clinical demonstrator at the Department of Radiotherapy, M.G.M. Medical College.

He served as a consultant radiation therapist at the N.P. Cancer Institute, Rajkot, India; and at Nanavati Hospital and Medical Research Center, Bombay, India.

Dr. Puranik completed a residency in the Department of Radiology, Radiation Oncology Division, SUNY Upstate Medical Center, Syracuse, NY, for which he was awarded a Fellowship in Radiation Oncology from the American Cancer Society. He was also a fellow in the Department of Radiation Oncology, Albany Regional Radiation Oncology Program, at Albany Medical College, where he was later named as assistant professor. Prior to his current venture, he was co-chair of the first prostate brachytherapy program in Upstate New York at Samaritan Hospital Cancer Treatment Center, Troy, New York. Dr. Puranik is board-certified in radiation oncology, and in 1997 received the Physician of the Year Award from the Capital District Chapter of the American Cancer Society.

Dr. Puranik has served the Board since July 1998.

NEETA SHAH, M.D., F.A.C.P.

Dr. Shah is vice president of women's health services at North Shore-Long Island Jewish Health System, overseeing coordination and expansion of services to ensure that the health system offers a range of clinical programs to meet women's life-long health care needs. A board-certified internist, she has served as vice chair of medicine and director of the internal medicine residency training program at Forest Hills Hospital, Queens, NY.

Dr. Shah also is adjunct clinical associate professor of medicine at New York College of Osteopathic Medicine, and has worked as clinical instructor in medicine at Cornell University Medical College.

Dr. Shah is a Fellow of the American College of Physicians (ACP) and a member of the American Medical Association, Association of Program Directors in Internal Medicine, and Association of Chairs and Chiefs of Medicine (ACCM). At present, she serves as president, New York State Program Directors in Internal Medicine; district president, Nassau East, New York Chapter, ACP; counselor, ACCM; and member, Residency Program Requirements Task Force and Workshop Selection Task Force, Alliance for Academic Internal Medicine.

At North Shore-Long Island Jewish, Dr. Shah is a member of the Institutional Review Board, Clinical Information Systems Steering Committee, Education Committee, and Academic Awards Committee, among other committee responsibilities. She has been accorded many honors, including The City of New York Certificate of Recognition, Citation of Honor from the Queens Borough President, New York State Assembly Citation, Certificate of Recognition and Gratitude from the New York City Council, 2008 Top Women in Queens Business Award, and the Physician Mentor Recognition Award from the American Medical Association Women's Physician Congress.

Dr. Shah received her medical education at J. N. Medical College, Belgaum, India; and completed her residency at Flushing Hospital Medical Center, Queens, NY.

Dr. Shah began serving the Board in December 2008.

ELINOR SPRING-MILLS, Ph.D.

Dr. Spring-Mills is a SUNY Distinguished Teaching Professor, and professor of cell and developmental biology and of urology at SUNY Upstate Medical University, Syracuse, NY. She holds a B.A. degree in physiology from Vassar College, an M.A. in physiology from Mount Holyoke College, and a Ph.D. in medical sciences (anatomy, biochemistry and pathology) from Harvard Medical School. She completed a postdoctoral fellowship at the NIH Division of Arthritis, Metabolic and Digestive Diseases, and then moved to San Francisco, where for seven years she was assistant chief of cell biology at the Veterans' Administration Hospital; and assistant and, subsequently, associate professor of anatomy at the University of California at San Francisco Medical School.

She has served as a member and chairperson of the Breast Cancer Working Group/Breast Cancer Task Force of the NCI; a founding member of the first Pan American Congress of Andrology; a member of the Educational Policies Committee, American Association of Anatomists; and interim chair of the Department of Anatomy at Upstate Medical School. In addition to publishing research papers and abstracts, she has co-edited three books on the accessory glands of the male reproductive tract and human prostatic cancer.

Dr. Spring-Mills has served the Board since May 2006.

JEAN WACTAWSKI-WENDE, Ph.D.

Dr. Wactawski-Wende is professor and associate chair of the Department of Social and Preventive Medicine, School of Public Health and Health Professions; and professor of gynecology-obstetrics, School of Medicine and Biomedical Sciences at SUNY at Buffalo. Dr. Wactawski-Wende is an epidemiologist with research interests in women's health. Her research is aimed at the study of risk factors for and prevention of osteoporosis, cancer and heart disease in women. She is also interested in hormonal effects on risk and prevention of disease. She has investigated calcium and vitamin D for the prevention of cancer and fractures. Among her research endeavors is the NIH-funded Women's Health Initiative, a clinical trial and observational study of postmenopausal women. She also is conducting a clinical trial of an aromatase inhibitor for the primary prevention of breast cancer. Dr. Wactawski-Wende received a Ph.D.in epidemiology from the University at Buffalo. She has been a member of the University at Buffalo faculty since 1989.

Dr. Wactawski-Wende served the Board from July 2002 until December 2008.

MARC WILKENFELD, M.D.

Dr. Wilkenfeld is a board-certified occupational/environmental physician working in New York City. He is an assistant professor in clinical medicine at Columbia University Medical Center, where he also serves as occupational medicine consultant to Columbia's Department of Environmental Health and Safety. He has lectured and trained internal medicine and family practice physicians on aspects of occupational/environmental medicine. Dr. Wilkenfeld also is an attending physician at New York Presbyterian Hospital and Beth Israel Medical Center. He has served as an occupational medicine consultant to corporations, government agencies and other organizations in the U.S. and Europe. He is past-president of the New York Occupational Medicine Association, and has lectured extensively in the field of occupational and environmental medicine.

Following the attacks of September 11, 2001, Dr. Wilkenfeld was named consultant to a number of government agencies, corporations and community groups on the environmental health impact of the disaster. In this role, he reviewed pre- and post-cleanup data and addressed questions regarding the potential health effects of contamination with World Trade Center dust. He moderated and participated in community forums designed to answer the health questions of residents and site workers. He also has evaluated cases of illness related to the disaster. Dr. Wilkenfeld serves as medical advisor to New York City Councilmember Alan Gerson, whose district includes Lower Manhattan. In this role, he continues to assist the Lower Manhattan Community with questions related to the health impacts of September 11.

Dr. Wilkenfeld has served the Board since September 2004.

B. Non-voting Members as of December 31, 2008

BEVERLY CANIN

Beverly Canin is a two-time breast cancer survivor. She is president of Breast Cancer Options, Inc. (BCO), a survivor-driven, community-based breast cancer support, education and advocacy organization in the Mid-Hudson Valley. She is a graduate of the NBCC Fund's Project LEAD, an intensive course for advocates on the basic science of breast cancer and on advocacy issues. She participates annually in the NBCC's Advocacy Training Conference and Lobby Day in Washington, D.C. Ms. Canin is the alternate representative from BCO to the Board of Directors of the New York State Breast Cancer Network, and the New York State Breast Cancer Support and Education Network, where she has chaired the Procedures Committee and is a member of the Access to Care Committee.

Ms. Canin has served as a consumer reviewer for the U.S. Department of Defense Breast Cancer Research Program since 2001 at both the peer-review and the programmatic review levels. She also has worked as an advocate reviewer for the California Breast Cancer Research Program. She is a member of Breast Cancer Action and of the Mid-Hudson Valley affiliate chapter of Sisters' Network, Inc.

Ms. Canin is retired, after having worked many years in non-profit administration, including as a consultant for program development and evaluation.

Ms. Canin began serving the Board in July 2008.

ROBERT RITER

Robert Riter's involvement with the breast cancer community began in 1996 when he was diagnosed with the disease at the age of 40. Unlike many men with breast cancer, Mr. Riter decided to go public about his diagnosis and did so by writing an essay about his experiences that appeared in the July 17, 1997, issue of *Newsweek* magazine.

Since 2000, Mr. Riter has been associate director of the Cancer Resource Center of the Finger Lakes (formerly known as the Ithaca Breast Cancer Alliance). He provides direct client services, offering information and support to people with all types of cancer. He also writes a regular column about living with cancer for the *Ithaca Journal*.

At the national level, Mr. Riter has served on scientific review panels at the U.S. Department of Defense Breast Cancer Research Program and the Susan G. Komen Breast Cancer Research Program. He has participated in Project LEAD and Project LEAD Quality Care training, sponsored by the NBCC, as well as the San Antonio Breast Cancer Symposium.

Prior to his work in cancer education and advocacy, Mr. Riter received an M.S. in hospital administration from the School of Public Health at the University of Michigan, and worked as a health care administrator before teaching health policy and health administration at Ithaca College.

Mr. Riter began serving the Board in July 2008.

C. *Ex-officio* Members

HEATHER C. DANTZKER, Ph.D.

Dr. Dantzker is a research associate with the Program on Breast Cancer and Environmental Risk Factors, Sprecher Institute for Comparative Cancer Research, Cornell University. She holds M.S. and Ph.D. degrees in the field of natural resources management from Cornell University, focusing on environmental toxicology and communication; and a B.A. in political economy from the University of California at Berkeley.

At Cornell, she applies her scientific and social-behavioral research findings to a variety of educational and outreach efforts for improving worker and public understanding of environmental health risks and cancer. Currently, her work is focused on the cancer risks associated with turf- and lawn-care pesticides. She authors cancer risk review articles, manages the online Cornell Turf Pesticides and Cancer Risk Database, and is co-principal investigator of the NY statewide research and extension project, "Turf and Lawn Care Professionals and Cancer: Improving Communication and Reducing Risk," funded by the U.S. Department of Agriculture's Cooperative State Research, Education, and Extension Service. She is an active member of the Society for Risk Analysis, the American Association of Pesticide Safety Educators, and the New York State Integrated Pest Management (IPM) Program's Community IPM Coordinating Council.

Dr. Dantzker was appointed as the Cornell University Institute for Comparative and Environmental Toxicology's designee to the Board in July 2008.

LAURENCE S. KAMINSKY, Ph.D.

Dr. Kaminsky is director of the DOH Wadsworth Center's Office of Environmental Research Development. He is also professor and chairman of the Department of Environmental Health Sciences at SUNY at Albany's School of Public Health. Dr. Kaminsky received a Ph.D. from the University of Cape Town, South Africa, and post-doctoral training at Yale University. He began his research career at the University of Cape Town Medical School. After a sabbatical year at SUNY at Albany, he joined the then-Division of Laboratories and Research of the DOH as a research scientist; and later became chief of Wadsworth's Laboratory of Human Toxicology and Molecular Epidemiology, and deputy director of Wadsworth's Division of Environmental Disease Prevention.

Dr. Kaminsky's research has focused on the drug metabolism enzymes – their regulation, function, polymorphisms and structures. These studies have resulted in approximately 200

papers in peer-reviewed journals and numerous invitations to lecture at international meetings. He is associate editor of two journals in this field, and serves as chair of the Drug Metabolism Division of the American Society of Pharmacology and Experimental Therapeutics, and on the executive committee of the International Society for the Study of Xenobiotics.

Dr. Kaminsky was appointed as the Commissioner of Health's designee to the Board in October 2006.

VAL WASHINGTON, Esq.

Val Washington is Deputy Commissioner for Remediation and Materials Management at the DEC. Previously, Ms. Washington, a graduate of Albany Law School, worked as senior policy analyst for New Partners for Community Revitalization, a not-for-profit organization that assists community organizations with neighborhood revitalization efforts. In addition to her current post, she has held a number of government positions since her graduation from law school, beginning with her appointment as Counsel to the New York State Olympic Task Force in 1979, and then as Regional Attorney for DEC's Region 3 Office in New Paltz, NY. She returned to Albany to take a position as Assistant Attorney General under Robert Abrams, and, for most of her 13-year tenure with the NYS Department of Law, held the title of Deputy Bureau Chief for its Environmental Protection Bureau. She left the Attorney General's Office in 1995 to become executive director of Environmental Advocates of New York, the State's primary environmental lobbying organization. After more than a decade of work in the non-profit sector, she returned to State government last May to accept her current appointment.

Ms. Washington was appointed as the DEC Commissioner's designee to the Board in November 2007.

D. Board Appointments

SANTO M. DIFINO, M.D. was reappointed to the Board as chair on June 3, 2008.

GAIL FRANKEL was appointed to the Board as a voting regional member (Long Island region) on July 1, 2008.

ALEXANDER P. GROSS, M.S., P.E. was appointed to the Board as a voting prostrate cancer survivor member on July 1, 2008.

M. SUZANNE HICKS, M.S.W. was appointed to the Board as a voting regional member (Northern region) on July 1, 2008.

DONNA JURASITS was appointed to the Board as a voting breast cancer survivor member on October 24, 2008.

GARY MORROW, Ph.D. was appointed to the Board as a voting member on December 4, 2008.

NEETA SHAH, M.D. was appointed to the Board as a voting member on December 28, 2008.

BEVERLY CANIN was appointed to the Board as a non-voting regional member (Hudson Valley region) on July 1, 2008.

ROBERT RITER was appointed to the Board as a non-voting regional member (Central New York region) on July 1, 2008.

HEATHER C. DANTZKER, Ph.D. was appointed to the Board as a non-voting *ex-officio* member (Cornell University) on July 21, 2008.

E. Changes in Membership

Members whose terms ended or who resigned during this reporting period include:

GERALDINE BARISH

Ms. Barish is a three-time breast cancer survivor and president of 1 in 9: The Long Island Breast Cancer Action Coalition. She lost her oldest son to Hodgkins' disease. A survivor-activist, she has spearheaded a spectrum of activities designed to expand scientific knowledge about the causes of breast cancer, especially the role of environmental factors in cancer etiology. Her efforts have helped secure national funding for the Long Island Breast Cancer Study Project, as well as enactment of State legislation creating the Pesticide Sales and Use Database, and the NYS HRSB itself.

Ms. Barish is executive director of Hewlett House, which provides support services to cancer victims, their families and friends. Nationally recognized for her leadership in the battle against breast cancer, she is the recipient of numerous national and State awards, including the National Organization of Women's Women of the Year Award and the first New York State Innovation in Breast Cancer Early Detection and Research Award. She is a member of the NBCC's Board of Directors, the New York State Breast and Cervical Cancer Advisory Council, Environmental Advocates, Nassau County Integrated Pest Management Advisory Board, and Nassau County Breast and Cervical Cancer Board. She is chair of the Nassau County Citizen's Advisory Cancer Task Force.

Ms. Barish served the Board as an *ex-officio* non-voting breast cancer survivor from 1998 until 2008.

PHILIP J. LANDRIGAN, M.D., M.Sc.

Dr. Landrigan is the Ethel H. Wise Professor, chair of the Department of Community and Preventive Medicine, and Director of Environmental and Occupational Medicine at the Mount Sinai School of Medicine in New York City. He holds a professorship in pediatrics at Mount Sinai, and directs the Mount Sinai Center for Children's Health and the Environment.

Dr. Landrigan obtained his medical degree from Harvard Medical School in 1967. He interned at Cleveland Metropolitan General Hospital, completed a residency in pediatrics at the Children's Hospital Medical Center in Boston, and then obtained a master's of science degree in occupational medicine and a diploma in industrial health from the University of London. He is board-certified in preventive medicine, pediatrics, and occupational /environmental medicine.

From 1970 to 1985, he served as a commissioned officer in the U.S. Public Health Service, as an epidemic intelligence service officer, and then as a medical epidemiologist with the U.S. Centers for Disease Control and Prevention (CDC), where he participated in epidemiologic studies of measles and rubella. He directed research and development activities for the CDC's Smallpox Eradication Program, and established and directed the Environmental Hazards Branch of CDC's Bureau of Epidemiology. Dr. Landrigan also worked for a year as a field

epidemiologist in El Salvador and for another year in northern Nigeria. From 1979 to 1985, as director of the Division of Surveillance, Hazard Evaluations and Field Studies of the NIH National Institute for Occupational Safety and Health, he headed the Institute's national program in occupational epidemiology.

Dr. Landrigan was the co-founder and then medical co-director of the Beacon Hill Community Clinic, a free-standing medical center established in partnership with community residents in Decatur, Georgia. He is a member of the prestigious Institute of Medicine of the National Academy of Sciences. He is editor-in-chief of the *American Journal of Industrial Medicine* and previously was editor of *Environmental Research*. He has chaired committees at the National Academy of Sciences on environmental neurotoxicology, and on pesticides in the diets of infants and children. He is chair of the Asbestos Advisory Board of the State of New York. In New York City, he worked on the Mayor's Advisory Committee to Prevent Childhood Lead Paint Poisoning, New York City Department of Health and Mental Hygiene. He is chair of the New York State Advisory Council on Lead Poisoning Prevention. From 1995 to 1997, he served on the Presidential Advisory Committee on Gulf War Veterans' Illnesses. During 1997 and 1998, he was a senior advisor on Children's Health to the Administrator of the U.S. Environment Protection Agency (EPA), where he was responsible for helping to establish a new Office of Children's Health Protection.

Dr. Landrigan served the Board from June 1997 until August 2008.

ALEXANDER YU. NIKITIN, M.D., Ph.D.

Dr. Nikitin is assistant professor of pathology in the Department of Biomedical Sciences at Cornell University. He received an M.D. degree in internal medicine from the Pavlov First Medical Institute, St. Petersburg, Russia, in 1983; and a Ph.D. in pathology from the Petrov Research Institute of Oncology, St. Petersburg, in 1988. Dr. Nikitin is a human pathologist by training. Prior to joining the Cornell faculty in 2000, he worked in cellular and molecular biology as a postdoctoral fellow and junior faculty at the Institute of Cell Biology and Tumor Research, Essen Medical School, Germany; and the Department of Molecular Medicine, University of Texas Health Science Center, San Antonio, Texas. His research has been supported by grants from the NIH and the U.S. Department of Defense.

Dr. Nikitin is a recipient of the National Center for Research Resources Midcareer Award in Mouse Pathobiology and serves as vice-chair of the Pathology and Laboratory Medicine Standing Committee of the Mouse Models of Human Cancer Consortium, NIH NCI. He is co-organizer of the Annual Practical Workshop Series on the Pathology of Mouse Models for Human Disease, held at the Jackson Laboratory, and Cornell and Purdue Universities.

His main research interests lie in modeling of human cancer in genetically modified mice, and studying early stages of carcinogenesis and metastasis in neoplasias of reproductive and endocrine systems. These studies have led to establishment of novel models of epithelial ovarian cancer and multiple endocrine neoplasias, and will allow for rational design and testing of tumor cell targeting based on functional identification of molecular and cellular markers of carcinogenesis.

Dr. Nikitin served the Board as the non-voting *ex-officio* Cornell University Institute for Comparative and Environmental Toxicology designee from 2003 until May 2008.

F. Vacancies

Despite the many appointments made in recent months, five Board vacancies remain, including: three voting scientists/researchers, one voting regional breast cancer survivor (Western NY), and one non-voting regional breast cancer survivor (New York City). Throughout the reporting period, vacancies played a major role in the ability of the Board to reach and maintain a quorum.

III. BOARD OPERATIONS

A. Meetings

PHL § 2411(1)(h) requires the Board to meet at least four times annually, and one of those meetings must be a public hearing. Meetings are announced at least two weeks in advance, and in accordance with Executive Order No. 3 of 2007, are now broadcast on the Internet, opening the proceedings to a wide audience. Agendas and approved minutes are posted on the Board program's Website at: http://www.wadsworth.org/extramural/breast cancer/, and are available upon request from the Board's Executive Secretary.

DOH staff dedicated a significant amount of time to planning, preparing for and facilitating Board meetings. These tasks include: agenda-setting; coordinating the needs and availability of Board members, public meeting sites, videoconferencing and Webcasting; issuing meeting notices; inviting speakers and arranging their travel; preparing reports; and recording accurate meeting minutes. During 2006, the Board adopted a meeting schedule to facilitate timely accomplishment of its mandates. Specifically, Board members agreed to convene for four meetings each year on a schedule that: 1) presents a scientific meeting/symposium to report the results of funded research; 2) includes the required annual public hearing; 3) allows standardized issuance dates for RFAs; and 4) permits timely issuance of this biennial report. As a result of changes in membership, which impaired the ability to meet a quorum, this schedule of activities was unable to be maintained during the 2007-2008 period (see table below). This situation resulted in significant delays in the conduct of Board business and program operations: breast cancer education community-based demonstration project awards were not able to be made in 2007, and two subsequent RFAs were not issued as planned in 2008. Following the appointment of several new voting members, the Board addressed these issues during its October 2008 meeting and approved a plan to make appropriate adjustments for the coming year. Meeting dates and locations have been standardized to allow members to plan their schedules well in advance. This plan will be facilitated by prompt appointment of the remaining six vacant positions.

DATE	BUSINESS MEETING	PUBLIC HEARING	LOCATION	VIDEOCONFERENCE SITES
January 5, 2007	X		DOH, Flanigan Square, Troy	NYC, Syracuse, Rochester and Buffalo
April 27, 2007 AM	X		DOH, Wadsworth Center, David Axelrod Institute, Albany	NYC, Syracuse, Rochester and Buffalo
April 27, 2007 PM	X	X	DOH, Wadsworth Center, David Axelrod Institute, Albany	NYC, Syracuse, Rochester and Buffalo
October 3, 2008 AM	X		DOH, 90 Church Street, New York City (NYC)	Not applicable
October 3, 2008 PM	X	X	DOH, 90 Church Street, NYC	Not applicable

B. Bylaws

At its October 3, 2008 afternoon meeting, the Board approved an amendment to the bylaws to allow for future expansion and enhanced performance of its standing committees, and management of the peer-review process via a contractor (Appendix VI).

C. Public Hearings

At the annual public hearings, in accordance with the Board's enabling legislation, the Commissioner's designee from the DEC provided a report (Appendix X) on the efficiency and utility of pesticide reporting established pursuant to ECL § 33-1205 and 33-1207 (see Appendix II). During the public hearings, interested parties may comment on the Board's operations, the Breast Cancer Research and Education Fund, the Prostate and Testicular Cancer Research and Education Fund, and pesticide reporting.

During the April 27, 2007 public hearing, Susan Cohen, chair of the New York State Breast Cancer Network, presented testimony regarding the Board's funding agenda, committee structure and Board structure. She asked the Board to support a bill to place advocates on the HRSB as voting members.

During the October 3, 2008 public hearing, Ms. Cohen gave a presentation on the Board's structure, funding agenda, availability of information regarding the Board's awards, committee structure and RFA requirements (see Appendix XV).

D. Other Public Comments

In addition to public hearings, a segment of each Board meeting is set aside for public comment. Synopses of comments from 2007-2008 Board meetings are presented below:

During the January 5, 2007 meeting, Cat Taylor, assistant vice president, AVP Oncology Services, South Nassau Communities Hospital, Oceanside, NY, informed the Board of cancer-related services offered by this full-scale cancer center on Long Island. The cancer center's program has been under development for five years. It provides education for cancer patients and serves a base population of 600,000. Ms. Taylor invited Board members to visit the program. An information packet about cancer-related services offered by the hospital was mailed to Board members. Dr. DiFino thanked Ms. Taylor for her efforts in raising awareness of cancer care in New York State.

At the January 5, 2007 meeting, William Smith, Cornell University, commented that whenever researchers request that confidential data be provided in a special format, some delay may be incurred because of the time needed for request processing. Dr. Nancy Kim, DOH staff support to the Committee on Access to Pesticide Registry and Pesticide Application Information, responded that she would send Mr. Smith and the Pesticide Sales and Use Database Committee members a copy of the request form for review and comment. A modification to the instructions to researchers may address this issue.

E. Reports to the Board

One of the Board's mandates is to "... consult with the Centers for Disease Control and Prevention, the National Institutes of Health, the Federal Agency for Health Care Policy and Research, the National Academy of Sciences and other organizations or entities which may be involved in cancer research to solicit both information regarding breast, prostate, and testicular cancer research projects that are currently being conducted and recommendations for future research projects...." [PHL § 2411 (1)(c)].

The Board monitors advances in the field, convenes symposia and solicits input and recommendations for future projects. The Committee on Research Needs and Education Program Effectiveness was established to assist the Board in fulfilling this mandate. However, this committee has been without members, and is thus inactive. At its October 2008 meeting, an Executive Session discussion highlighted the need to revitalize the Committee structure now that Board membership is becoming more stable.

F. Symposium

Symposia provide a scientific networking venue for postdoctoral fellows and their mentors, researchers, Board members, advocates, public health officials, and others. The meetings increase public awareness of important scientific discoveries, such as those achieved in breast cancer research.

The HRSB symposium, "Advancing Breast Cancer in New York State," was held in Albany, NY, on October 26, 2007. The meeting was well attended by some 40 researchers and clinicians. Board members present actively engaged in interacting with the fellows about their work and expressed strong interest in making this a biennial event.

The Board invited abstracts from the 29 promising postdoctoral fellows supported by the New York State Breast Cancer Research and Education Fund at the time. The abstracts demonstrated that the Board has been successful in funding a wide range of breast cancer research activities. During the symposium, five of the fellows were asked to give a brief summary of the spectrum of the research underway. Several fellows also gave poster sessions to discuss their research findings.

Abstracts from the symposium presentations can be found in Appendix VIII.

IV. PROGRAM FUNDS

The Breast Cancer Research and Education Fund supports grant contracts issued by the DOH on behalf of the Board. The Fund is financed by donations made by individuals and corporations on State income tax forms, direct gifts to the Fund, and one-half of the proceeds from sales of Drive for the Cure specialty license plates (Tax Law § 209-D and 627; and Vehicle and Traffic Law § 404-q). In 2000, New York State began matching, dollar-for-dollar, income tax donations made to the Fund.

Deposits to the Fund since its inception in 1996 are presented below. Gifts from the previous tax year are collected in the current year.

Calendar Year	Tax Year	Tax Return Donations	License Plates Income	Matching Funds	Interest (State Fiscal Year)	Cumulative Revenues
1997	1996	$686,689	$0	$0	$3	$686,692
1998	1997	$524,185	$0	$0	$28,403	$1,239,280
1999	1998	$593,321	$0	$0	$60,571	$1,893,172
2000	1999	$642,794	$1,900	$642,794	$85,499	$3,266,159
2001	2000	$620,040	$35,094	$621,940	$119,114	$4,662,347
2002	2001	$592,886	$18,263	$627,980	$79,405	$5,980,880
2003	2002	$532,389	$55,750	$550,652	$52,056	$7,171,727
2004	2003	$545,629	$29,038	$601,379	$36,127	$8,383,899
2005	2004	$529,646	$58,213	$558,684	$55,013	$9,585,455
2006	2005	$541,417	$28,618	$599,630	$156,285	$10,911,404
2007	2006	$547,807	$47,443	$576,425	$292,431	$12,375,510
Through 11/30/2008	2007	$561,235	$17,038		$92,874	$13,046,660
Totals		**$6,918,038**	**$291,357**	**$4,779,484**	**$1,057,781**	**$13,046,660**

V. MAJOR DUTIES OF THE BOARD AND PROGRAM

The Board's operations and activities address two major responsibilities: (1) awarding grants for research and education projects; and (2) advising on pesticide-related issues and overseeing the Pesticide Sales and Use Database.

A. Research and Education

1. Awards for Breast Cancer Research and Education Projects

In keeping with its mandate, the Board solicits, receives, and reviews applications from public and private agencies, and organizations and qualified research institutions for grants supported by the Breast Cancer Research and Education Fund. Research or educational programs recommended for support to the Commissioner of Health focus on the causes, prevention, screening, treatment and cure of breast cancer. A variety of investigative approaches may be funded, including, but not limited to, basic, behavioral, clinical, demographic, environmental, epidemiologic and psychosocial research. Since its first grant

competition in 1998, the Board has recommended 88 research and education projects for funding, and the DOH has committed $8,050,012 to support these programs via contracts.

A contractor training session was held in April 2007 to facilitate communications among contractors and DOH program staff, and provide guidance on the contracting, vouchering and reporting processes. More than 20 contract-related staff attended from eight institutions. This training has resulted in improved communication channels and enhanced timely and accurate responses from contractors on various contract requirements. In 2008, materials and resources were posted on the DOH Website to assist contractors with various compliance and reporting activities required under contract. Funds awarded since the Program's inception are detailed below:

YEAR	FUNDS COMMITTED	FUNDS DISBURSED	AWARDS
1998	$1,461,892	$1,087,985	18 EMPIRE (EMPowerment Through Innovative Research and Education) Awards and 9 Postdoctoral Fellowship Awards
2001	$2,700,000	$2,669,152	19 EMPIRE Awards and 8 Postdoctoral Fellowship Awards
2002	$299,998	$188,821	4 Community-Based Organization Demonstration Awards
2004	$3,588,122	$3,100,289	30 Postdoctoral Fellowship Awards
TOTAL	$8,050,012	$7,046,247	88 Awards

2. Requests for Applications

The 2004 Postdoctoral Fellowship Awards (Appendix VII) were scheduled to be completed by December 31, 2007. However, due to late contract start-up, 11 contractors requested and received no-cost time extensions to continue their work in 2008. These contracts have now ended. Issuance of RFAs at the same time each year is now planned for consistent expenditures of the Breast Cancer Research and Education Fund. Standardized issuance of RFAs will provide successful applicants with consistent contract start dates for ease of management of their laboratories, resources and funds.

Expansion and stabilization of the Board and its research and education programs were undertaken in 2007-2008. Unfortunately, the Board's inability to meet a quorum for several meetings prevented Board authorization to issue these RFAs until October 2008. The DOH expects to issue these RFAs in 2009.

The Peter T. Rowley Research Program (formerly EMPIRE) RFA will supply initial support for preliminary testing of novel or exploratory hypotheses related to breast cancer. Investigators are to open a new area of investigation, satisfactorily test a novel or innovative hypothesis, or produce viable data for preparation of a full-scale research application to another organization.

The Postdoctoral Fellowship RFA will support continued training of basic or clinical investigators with exceptional potential for making significant contributions to the field of breast cancer research.

The Patricia S. Brown Community-Based Organization (CBO) Education Demonstration Projects RFA will invite applications from CBOs in collaboration with researchers from accredited academic institutions, including medical centers, medical schools, teaching hospitals, universities and schools of public health, for planning and assessment of new breast cancer education programs and materials. It is intended that collaborations among CBOs and academic institutions fostered by this funding program will lead to education projects that are: 1) appropriate to communities; 2) medically and scientifically accurate; and 3) demonstrably effective in increasing knowledge and promoting healthy behaviors.

3. Program Outreach and Visibility

As a strategy to encourage interest in the Board's program, brochures on the Board's mission, Board members, as well as recipients of 2006 Breast Cancer Research Postdoctoral Fellowship Awards and their mentors, were updated and distributed to academic research institutions, Board members, past and present contractors, and other interested parties.

The DOH's Wadsworth Center Website at: http://www.wadsworth.org/extramural/breastcancer has been updated to make it more descriptive and easier to search. Reference materials have been placed on the Website to assist researchers and administrators with contract compliance, progress reporting and fiscal management. E-alerts is a new feature that allows interested parties to receive notification of Board activities such as RFA issuances, event announcements, news releases and grants awarded. These enhanced communication tools for the public, potential applicants and contractors are expected to increase interest in, support for and visibility of, the program.

4. Peer Review

In October 2008, the Board approved changes to the bylaws allowing a contractor to manage the peer-review process for funding applications. An external peer-review process is intended to: 1) remove Board members from the peer review process, reducing the perception of possible conflicts of interest; 2) allow independent peer reviews in a timely manner by expert scientists, clinicians, educators and others with the appropriate expertise; and 3) allow staff to focus on program management. Staff is to oversee each peer review meeting to ensure that applicants receive the benefit of the highest quality reviews.

A Request for Proposals was developed to solicit applications for the peer review, and a contractor selected. The contract is proceeding through the approval and execution process.

B. Pesticide-Related Activities

Copies of any reports or information about the Board's pesticide-related activities may be obtained by calling the DOH toll-free at 1(800) 458-1158, and providing the Board's name and report/document title.

1. Pesticide Data Collection and Access

Confidential information from the Pesticide Use and Sales Database (also known as the Pesticide Registry) collected by the DEC and pesticide application information maintained by private applicators are, with certain restrictions, available to scientists involved in human health-related research. Any information, such as a name and address that could identify a commercial or private pesticide applicator, including a farmer or anyone who receives the services of a commercial applicator, is considered confidential information. Researchers seeking confidential pesticide registry information or pesticide application information should contact the DOH toll-free at 1(800) 458-1158, extension 2-7820. The following researcher access documents will be provided: Request for Pesticide Registry or Pesticide Application Information; Guidelines to Restrict the Dissemination by Researchers of Confidential Pesticide Registry and Pesticide Application Information; Agreement to Maintain Confidentiality; Additional Information Concerning the Confidentiality Plan; and an information sheet that summarizes these documents in lay language.

2. Committee on Access to Pesticide Registry and Pesticide Application Information

During 2007-2008, Mr. Patrick Hooker, a member of the Committee on Access to Pesticide Registry and Pesticide Application Information representing the New York Farm Bureau, resigned to accept an appointment as Commissioner of the New York State Department of Agriculture and Markets. Mr. Jeffrey Williams of the New York Farm Bureau was named to the Committee as Mr. Hooker's replacement. Dr. Heather Dantzker of the Program on Breast Cancer and Environmental Risk Factors at Cornell University was appointed to the Committee to replace Dr. Philip Landrigan, who resigned effective August 25, 2008.

The Board is charged with reviewing requests for access to the confidential pesticide information collected. The Board's bylaws designate the Committee on Access to Pesticide Registry and Pesticide Application Information as one of its standing committees. The Committee is comprised of representatives from stakeholder groups with various perspectives and areas of expertise, including breast cancer advocacy, chemical pesticides, commercial pesticide application, and private pesticide application. Appendix XI lists the Committee's charge and the members as of December 2008.

In sum, the Committee is responsible for reviewing requests for Pesticide Registry and pesticide application information for use in human health-related research projects. The Committee makes recommendations to the full Board for final action. The entire review process requires four to six months.

3. Applications for Confidential Pesticide Registry Information Received During 2007-2008

One application for confidential pesticide registry information underwent the Pesticide Committee's review process during 2006. The application, "Surveying Upstate New York Well Water for Pesticide Contamination (Cayuga and Orange Counties)," was submitted by Tammo Steenhuis, Ph.D., of the Cornell University Department of Biological and Environmental Engineering. The Board considered the application early in 2007. The Board approved the request, and the data have been provided to the researcher. The abstract of this research project and contact information for the researcher are found in Appendix XII.

4. Evaluation of the Basis, Efficiency and Scientific Utility of the Information Derived from Pesticide Reporting

The biennial report submitted to the Legislature by the Board must include, "…an evaluation … of the basis, efficiency and scientific utility of the information derived from pesticide reporting," as well as recommendations as to, "…whether such system should be modified or continued." The Board is also instructed to consider, "… whether private citizen use of residential pesticides should be added to the reporting requirements."

For previous reports, the Board surveyed interested parties, including environmental groups, breast cancer advocacy groups, government agencies, academic entities, and business and trade groups. Two surveys have been conducted (during 2000 and 2002-03). These previous surveys showed that the pesticide data have been used to determine overall patterns of pesticide use in the State for: mapping; targeting the development of education programs on farmworker safety and health, or integrated pest management/pesticide use reduction; answering questions from the public or organizations about pesticide use; and water quality assessment.

In April 2007, staff from the DEC and DOH reported to the Board on how these agencies were using the pesticide sales and use data. DEC reported application of the pesticide data to: make decisions related to registration of pesticides; assess groundwater; and identify areas for additional outreach to emphasize use of less toxic alternatives and areas for additional training. The database has also been used to track restricted-use products and to identify inactive pesticide applicators. The DEC Marine Resources Division reviewed the database to evaluate any correlation with a recent lobster die-off; none was found.

DOH reported on use of the pesticide data in the Coram-Mt. Sinai-Port Jefferson investigation, a followup on DOH's maps of breast cancer incidence for 1993-1997 showing elevated rates in this area. Many risk factors were reviewed during the investigation, including pesticide application. DOH also described the Environmental Public Health Tracking Program, part of an initiative developed and supported by the U.S. Centers for Disease Control and Prevention involving many states. The Program looks at changes in health, hazard, and exposure data over time and in various geographic areas. An example of the value of the pesticide sales and use data in New York's Program focused on turfgrass herbicides, a category of pesticide products with the greatest use and sales in New York State. It was shown that the data could be refined to examine an active ingredient, such as 2,4-D; that data from other sources, such as the U.S. Census, could be added; and that ZIP code-level data could be studied.

During 2007-2008, significant modifications and enhancements were made to the Pesticide Sales and Use Reporting Website (http://pmep.cce.cornell.edu/psur/). One suggestion from the 2000 survey and made again in 2006 was to improve the usefulness of the pesticide data by expressing the data in pounds of active ingredient, as well as amount of pesticide product. An active ingredient search function that allows multi-year searching capabilities and flexibility in selecting ZIP codes for searches has been added to the Website. This new search function is also responsive to a comment from 2002-03 requesting that the Website be modified for ease of use and flexibility of reporting. Documents also were added to the site to assist the user in searching the pesticide product database. These documents include Frequently Asked Questions, a data dictionary and a glossary.

To solicit comments on the benefits of these changes to the Website, an interactive survey form was developed and posted on the Website in July 2008. An outreach letter describing these changes and the availability of the survey form online was distributed by mail and e-mail

to about 575 interested parties, including respondents to the earlier surveys, requestors of the data, academic organizations, environmental groups, breast cancer advocacy groups, government agencies, and business and trade groups. The outreach letter can be found in Appendix XIV. At this time, responses to the survey are still being accepted. Ultimately, recommendations will be developed based on the responses received.

5. Board Reports on Pesticide-Related Topics and on Studies Using or Referring to the Pesticide Sales and Use Database

The Board has released the following reports on pesticide-related topics since its inception. The legislative mandates for the reports are noted in parentheses:

- Data Sets Collected and Maintained by New York State Government That May Assist Researchers Engaged in Breast, Prostate or Testicular Cancer Research, January 1999 [PHL § 2412(a) and (b)].

- Pesticide Use and Pesticide Exposure, May 1999 [PHL § 2411(1)(f)].

- Reference List: Pesticide Use and Pesticide Exposure, May 1999 [PHL § 2411(1)(f)]; Reference List: Pesticide Use and Pesticide Exposure, September 2002 [PHL § 2411(1)(f)].

- Comparison of Pesticide Reporting and Pesticide Use, February 2000 [PHL § 2411(1)(g)].

- Survey Results and Recommendations – Pesticide Reporting Law, February 2001 (PHL § 2413).

- Results of the 2002-2003 Survey on Pesticide Reporting and Board Recommendations, March 2005 (PHL § 2413).

The Board recommended in 2004 that each biennial report should include references to studies that have been stimulated or influenced by the pesticide database. No reports were issued during 2007-2008 referring to the Pesticide Sales and Use Database.

Appendix XIII lists the Board's recommendations on pesticide reporting based on surveys of interested parties in 2000 and 2002-2003, as well as recommendations from users of the data in 2006. Summaries of progress achieved as a result are also included.

APPENDICES I - XV

APPENDIX I

PUBLIC HEALTH LAW
ARTICLE 24
TITLE 1-B
HEALTH RESEARCH SCIENCE BOARD
As amended by Chapter 32 of the Laws of New York, 2008

§ 2410. Health research science board.
1. There is hereby established in the department the health research science board. The board shall be comprised of seventeen voting members, three non-voting regional members and three non-voting ex-officio members as follows:

(a) twelve voting members shall be scientists each of whom shall have either an M.D., D.O., Ph.D., or Dr.P.H. in one of the following fields: biochemistry, biology, biostatistics, chemistry, epidemiology, genetics, immunology, medicine, microbiology, molecular biology, nutrition, oncology, reproductive endocrinology, or toxicology and must currently be engaged in treating patients or conducting health research. Such members shall be appointed in the following manner: two shall be appointed by the temporary president of the senate and one by the minority leader of the senate; two shall be appointed by the speaker of the assembly and one by the minority leader of the assembly; six shall be appointed by the governor;

(b) the governor shall appoint six regional members, three of whom shall serve as full voting members and three of whom shall serve as alternative members without voting rights. Such regional members shall be persons who have or have had breast cancer, and shall be actively involved with a community-based, grass-roots breast cancer organization. Two of such appointments shall be made upon the recommendation of the temporary president of the senate and two shall be made upon the recommendation of the speaker of the assembly. One regional member shall
be appointed from each of the following geographic areas of the state: Long Island, New York City, the Hudson Valley, Northern New York, Central New York and Western New York. The order of appointments and recommendations for appointments and voting rights shall rotate as follows:

i) The governor shall appoint regional members for three year terms in the following order:
(A) Long Island, which member shall have voting rights,
(B) Central New York, which member shall not have voting rights,
(C) Hudson Valley, which member shall have voting rights,
(D) Northern New York, which member shall not have voting rights,
(E) Western New York, which member shall have voting rights, and
(F) New York City, which member shall not have voting rights;

(ii) The governor, upon the recommendation of the temporary president of the senate, shall appoint regional members for three year terms in the following order:
(A) Hudson Valley, which member shall not have voting rights,

(B) Northern New York, which member shall have voting rights,
(C) Western New York, which member shall not have voting rights,
(D) New York City, which member shall have voting rights,
(E) Long Island, which member shall have voting rights, and
(F) Central New York, which member shall not have voting rights; and

(iii) The governor, upon the recommendation of the speaker of the assembly, shall appoint regional members for three year terms in the following order:
(A) Western New York, which member shall have voting rights,
(B) New York City, which member shall not have voting rights,
(C) Long Island, which member shall not have voting rights,
(D) Central New York, which member shall have voting rights,
(E) Hudson Valley, which member shall not have voting rights, and
(F) Northern New York, which member shall have voting rights;

(c) The governor shall appoint three non-voting ex officio members to the board, one of whom shall be the commissioner, or his or her designee, one of whom shall be the commissioner of environmental conservation, or his or her designee, and one of whom shall be the director of the Cornell University Institute for Comparative and Environmental Toxicology, or his or her designee; and

(d) The governor shall appoint one voting member who shall be a person who has or has survived breast cancer and one voting member who shall be a person who has or has survived prostate or testicular cancer. The governor shall designate the chair of the board. The governor, temporary president of the senate, minority leader of the senate, speaker of the assembly, and minority leader of the assembly may solicit
recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, the Federal Agency For Health Care Policy and Research, and the National Academy of Sciences for appointments or recommendations for appointments to the board.

2. All members shall serve for terms of three years and may be reappointed, such terms to commence July first and expire June thirtieth; provided, however, that of the scientific members first appointed, three such members, one appointed by the governor, one appointed by the temporary president of the senate and one appointed by the speaker of the assembly, shall be appointed for terms of one year, and three such members, one appointed by the governor, one appointed by the temporary president of the senate, and one appointed by the speaker of the assembly shall be appointed for a term of two years.

The board shall convene on or before September first, nineteen hundred ninety-seven.

3. Any member, after notice and an opportunity to be heard, may be removed by the governor for neglect of duty or malfeasance in office. Any member who fails to attend three consecutive meetings of the board, unless excused by formal vote of the board, shall be deemed to have vacated his or her position.

4. Any vacancy in the board shall be filled for the unexpired term in the same manner as the original appointment.

5. A majority of the voting members of the board shall constitute a quorum for the transaction of any business or the exercise of any power or function of the board.

6. Members of the board shall not receive compensation for their services as members, but shall be allowed their actual and necessary expenses incurred in the performance of their duties.

7. For the purposes of this section the following counties shall constitute the following geographic areas:

(a) Long Island: the counties of Nassau and Suffolk.

(b) New York City: the counties of Kings, Queens, Richmond, New York and Bronx.

(c) Hudson Valley: the counties of Westchester, Rockland, Putnam, Orange, Dutchess, Ulster, Greene, Columbia, Sullivan and Delaware.

(d) Northern New York: the counties of Albany, Clinton, Essex, Franklin, Fulton, Herkimer, Hamilton, Montgomery, Otsego, Rensselaer, Saratoga, Schenectady, Schoharie, Warren and Washington.

(e) Central New York: the counties of Broome, Cayuga, Chemung, Chenango, Cortland, Jefferson, Lewis, Madison, Oneida, Onondaga, Oswego, Seneca, Schuyler, St. Lawrence, Tioga, Tompkins and Wayne.

(f) Western New York: the counties of Allegany, Cattaraugus, Chautauqua, Erie, Genesee, Niagara, Orleans, Wyoming, Livingston, Monroe, Ontario, Steuben and Yates.

§ 2411. Powers and duties of the board.

1. The board shall:

(a) Survey state agencies, boards, programs and other state governmental entities to assess what, if any, relevant data has been or is being collected which may be of use to researchers engaged in breast, prostate or testicular cancer research;

(b) Consistent with the survey conducted pursuant to paragraph (a) of this subdivision, compile a list of data collected by state agencies which may be of assistance to researchers engaged in breast, prostate or testicular cancer research as established in section twenty-four hundred twelve of this title;

(c) Consult with the Centers for Disease Control and Prevention, the National Institutes of Health, the Federal Agency For Health Care Policy and Research, the National Academy of Sciences and other organizations or entities which may be involved in cancer research to solicit both information regarding breast, prostate and testicular cancer research projects that are currently being conducted and recommendations for future research projects;

(d) Review requests made to the commissioner for access to information pursuant to paragraph b of subdivision one of section 33-1203 and paragraph c of subdivision two of section 33-1205 of the environmental conservation law for use in human health related research projects. Such data shall only be provided to researchers engaged in human health related research. The request made by such researchers shall include a copy of the research proposal or the research protocol approved by their institution and copies of their institution's Institutional Review Board (IRB) or equivalent review board approval of such proposal or protocol. In the case of research conducted outside the auspices of an institution by a researcher previously published in a peer-reviewed scientific journal, the board shall request copies of the research proposal and shall deny access to the site-specific and nine-digit zip code pesticide data if the board determines that such proposal does not follow accepted scientific practice for the design of a research project. The board shall establish guidelines to restrict the dissemination by researchers of the name, address or other information that would otherwise identify a commercial applicator or private applicator or any person who receives the services of a commercial applicator;

(e) Solicit, receive, and review applications from public and private agencies and organizations and qualified research institutions for grants from the breast cancer research and education fund, created pursuant to section ninety-seven-yy of the state finance law, to conduct research or educational programs which focus on the causes, prevention, screening, treatment and cure of breast cancer and may include, but are not limited to basic, behavioral, clinical, demographic, environmental, epidemiologic and psychosocial research. The board shall make recommendations to the commissioner, and the commissioner shall, in his or her discretion, grant approval of applications for grants from those applications recommended by the board. The board shall consult with the Centers for Disease Control and Prevention, the National Institutes of Health, the Federal Agency For Health Care Policy and Research, the
National Academy of Sciences, breast cancer advocacy groups, and other organizations or entities which may be involved in breast cancer research to solicit both information regarding breast cancer research projects that are currently being conducted and recommendations for future research projects. As used in this section, "qualified research institution" may include academic medical institutions, state or local
government agencies, public or private organizations within this state, and any other institution approved by the department, which is conducting a breast cancer research project or educational program. If a board member submits an application for a grant from the breast cancer research and education fund, he or she shall be prohibited from reviewing and making a recommendation on the application;

(f) Consider, based on evolving scientific evidence, whether a correlation exists between pesticide use and pesticide exposure. As part of such consideration the board shall make recommendations as to methodologies which may be utilized to establish such correlation;

(g) After two years of implementation of pesticide reporting pursuant to section 33-1205 of the environmental conservation law, the board shall compare the percentage of agricultural crop production general use pesticides being reported to the total amount of such pesticides being used in this state as estimated by Cornell University, Cornell Cooperative Extension, the department of environmental conservation, and
the Environmental Protection Agency;

(h) Meet at least six times in the first year, at the request of the chair and at any other time as the chair deems necessary. The board shall meet at least four times a year thereafter. Provided, however, that at least one such meeting a year shall be a public hearing, at which the general public may question and present information and comments to the board with respect to the operation of the health research science board, the breast cancer research and education fund, the prostate and testicular cancer research and education fund and pesticide reporting established pursuant to sections 33-1205 and 33-1207 of the environmental conservation law. At such hearing, the commissioner of the department of environmental conservation or his or her designee shall make a report to the board with respect to the efficiency and utility of pesticide reporting established pursuant to sections 33-1205 and 33-1207 of the environmental conservation law.

2. The commissioner shall request that the department of environmental conservation compile information pursuant to paragraph b of subdivision one of section 33-1203 of the environmental conservation law as necessary to fulfill board approved requests, pursuant to paragraph (d) of subdivision one of this section.

3. The commissioner shall provide the board with such staff assistance and support services as are necessary for the board to perform the functions required of it under this section.

§ 2412. Agency implementation. All state agencies, including, but not limited to, the departments of agriculture and markets, environmental conservation, and health, shall review their programs and operations (pursuant to guidelines established by the board) to determine whether they currently collect data which may be of use to researchers engaged in breast, prostate or testicular cancer research. Any agency collecting such data shall forward a description of the data to the health research science board.

§ 2413. Biennial report. The commissioner shall submit a report on or before January first commencing in nineteen hundred ninety-nine, and biennially thereafter, to the governor, the temporary president of the senate and the speaker of the assembly concerning the operation of the health research science board. Such report shall include recommendations from the health research science board including, but not limited to, the types of data that would be useful for breast, prostate or testicular cancer researchers and whether private citizen use of residential pesticides should be added to the reporting requirements. The report shall also include a summary of research requests granted or denied. In addition, such report shall include an evaluation by the commissioner, the commissioner of the department of environmental conservation and the health research science board of the basis, efficiency and scientific utility of the information derived from pesticide reporting pursuant to sections 33-1205 and 33-1207 of the environmental conservation law and recommend whether such system should be modified or continued. The report shall include a summary of the comments and recommendations presented by the public at the board's public hearings.

APPENDIX II

ENVIRONMENTAL CONSERVATION LAW
TITLE 7: REGISTRATION OF PESTICIDES
TITLE 12: PESTICIDE SALES AND USE DATA BASE AND RECORDKEEPING AND REPORTING

§ 33-0714. Water quality monitoring for pesticides.

The department, in coordination with the United States Geological Survey, National Water Quality Assessment Program, the New York State Water Resources Institute, and other parties, shall conduct a water quality monitoring program to provide an adequate understanding of the health and environmental impacts of pesticide use in the state. The department shall utilize this program, as it deems necessary, in: making pesticide registration decisions; reviewing suspensions and cancellations of pesticide registrations in the state; and assessing the status, trends, and health impacts of any pesticide contamination of ground and surface waters on Long Island and throughout the state.

§ 33-1201. Pesticide sales and use computer data base.

1. a. The department shall develop a pesticide sales and use computer data base in conjunction with Cornell University. The data base shall be maintained at the department.
b. Such data base shall consist of all information compiled from reports submitted to the department pursuant to sections 33-1205 and 33-1207 of this title. Such reports shall be entered into and maintained on a computerized data base and shall be updated annually. Information obtained for and contained in the data base shall be accessible by interested parties only to the extent permitted pursuant to the provisions of subdivision two of this section and paragraph a of subdivision 1 of section 33-1203 of this title.

2. The commissioner shall prepare an annual report summarizing pesticide sales, quantity of pesticides used, category of applicator and region of application. The commissioner shall not provide the name, address, or any other information which would otherwise identify a commercial or private applicator, or any person who sells or offers for sale restricted use or general use pesticides to a private applicator, or any person who received the services of a commercial applicator. In accordance with article six of the public officers law, proprietary information contained within such record, including price charged per product, shall not be disclosed. The report shall be submitted to the governor, the temporary president of the senate and the speaker of the assembly, and shall be made available to all interested parties. The first report shall be submitted on July first, nineteen hundred ninety-eight and on July first annually thereafter.

§ 33-1203. Access to pesticide information.

1. a. The commissioner shall, upon written request of an interested party, in printed form or on a diskette in computerized data base format, provide the information on pesticides submitted to the department pursuant to sections 33-1205 and 33-1207 of this title. Such information shall be provided by county or counties, or five-digit zip code or codes as selected by the interested

party making the written request. The commissioner shall not provide the name, address, or any other information which would otherwise identify a commercial or private applicator, or any person who sells or offers for sale restricted use or general use pesticides to a private applicator, or any person who received the services of a commercial applicator. In accordance with article six of the public officers law, proprietary information contained within such record, including price charged per product, shall not be disclosed. The provisions of this paragraph shall not apply to the provision of pesticide data to the commissioner of health, the health research science board and researchers pursuant to title one-B of article twenty-four of the public health law.

b. The department shall, upon request from the department of health, compile pesticide application information by nine-digit zip code and provide the information to the commissioner of health for researchers entitled to receive information pursuant to paragraph (d) of subdivision one of section twenty-four hundred eleven of the public health law provided, however, if the nine-digit zip code cannot be determined, the information shall be compiled by town or city.

2. The fees for copies of information shall not exceed twenty-five cents per photocopy not in excess of nine inches by fourteen inches, or the actual cost of reproducing any information.

§ 33-1205. Recordkeeping and reporting.

1. All commercial applicators shall maintain pesticide use records for each pesticide application containing the following:

a. EPA registration number;

b. product name;

c. quantity of each pesticide used;

d. date applied;

e. location of application by address (including five-digit zip code).

Such records shall be maintained for a period of not less than three years. All commercial applicators shall file, at least annually, a report or reports containing such information with the department on computer diskette or in printed form on or before February first for the prior calendar year. All commercial applicators shall also maintain corresponding records of the dosage rates, methods of application and target organisms for each pesticide application. These records shall be maintained on an annual basis and retained for a period of not less than three years and shall be available for inspection upon request by the department.

2. a. Every person who sells or offers for sale restricted use pesticides to private applicators shall issue a record to the private applicator of each sale of a restricted use pesticide or a general use pesticide used in agricultural crop production to such applicator. Such record of each sale shall include the following:

1. EPA registration number;

2. product name of the pesticide purchased;

3. quantity of the pesticide purchased;

4. date purchased;

5. location of intended application by address (including five-digit zip code) or if address is unavailable by town or city (including five-digit zip code) if the location of intended application differs from the billing address that appears on the record.

Every person who sells or offers for sale restricted use pesticides to private applicators shall file, at least annually, a report or reports containing such information with the department on computer diskette or in printed form on or before February first for the prior calendar year. The department shall not use the reports filed pursuant to this paragraph for enforcement purposes.

b. All private applicators shall maintain, at a minimum, records of the restricted pesticides purchased, crop treated by such, method of application, and date of application or applications.

This information shall be maintained on an annual basis and retained for a minimum of three years, and shall be available for inspection upon request by the department.

c. A private applicator shall, upon request, within six months, provide site-specific information relating to pesticide applications to any researcher entitled to receive information pursuant to paragraph (d) of subdivision one of section twenty-four hundred eleven of the public health law, provided, however, such request shall not be granted during planting and harvesting unless at a time and in a manner that is mutually convenient.

§ 33-1207. Recordkeeping and reporting by importers and manufacturers.

1. Each person manufacturing or compounding a registered restricted use pesticide in this state, or importing or causing a registered restricted use pesticide to be imported into this state for use, distribution, or storage, shall maintain records of all sales within the state during the preceding year of each restricted use pesticide product which he or she has imported, manufactured or compounded. The record of each restricted use pesticide product shall include:

a. EPA registration number;

b. container size; and

c. number of containers sold to New York purchasers.

2. Such records shall be maintained for a period of not less than three years. All manufacturers and importers shall file an annual report containing such information with the department on computer diskette or in printed form on or before February first for the prior calendar year.

APPENDIX III

STATE FINANCE LAW
Article 6

§ 97-yy. Breast cancer research and education fund.

1. There is hereby established in the joint custody of the commissioner of taxation and finance and the comptroller, a special fund to be known as the "breast cancer research and education fund".

2. Such fund shall consist of all revenues received by the department of taxation and finance, pursuant to the provisions of section two hundred nine-D and section six hundred twenty-seven of the tax law, all moneys collected pursuant to section four hundred four-q of the vehicle and traffic law, and all other moneys appropriated, credited, or transferred thereto from any other fund or source pursuant to law. For each state fiscal year, there shall be appropriated to the fund by the state, in addition to all other moneys required to be deposited into such fund, an amount equal to the amounts of monies collected and deposited into the fund pursuant to sections two hundred nine-D and six hundred twenty-seven of the tax law and section four hundred four-q of the vehicle and traffic law during the preceding calendar year, as certified by the comptroller. Nothing contained herein shall prevent the state from receiving grants, gifts or bequests for the purposes of the fund as defined in this section and depositing them into the fund
according to law.

2-a. On or before the first day of February each year, the comptroller shall certify to the governor, temporary president of the senate, speaker of the assembly, chair of the senate finance committee and chair of the assembly ways and means committee, the amount of money deposited in the breast cancer research and education fund during the preceding calendar year as the result of revenue derived pursuant to sections two hundred nine-D and six hundred twenty-seven of the tax law and section four hundred four-q of the vehicle and traffic law.

3. Monies of the fund shall be expended only for breast cancer research and educational projects. As used in this section, "breast cancer research and education projects" means scientific research or educational projects which, pursuant to section two thousand four hundred eleven of the public health law, are approved by the department of health, upon the recommendation of the health research science board.

4. Monies shall be payable from the fund on the audit and warrant of the comptroller on vouchers approved and certified by the commissioner of health.

5. To the extent practicable, the commissioner of health shall ensure that all monies received during a fiscal year are expended prior to the end of that fiscal year.

APPENDIX IV

STATE TAX LAW
Article 9-A

§ 209-D. Gift for breast cancer research and education. Effective for any tax year commencing on or after January first, nineteen hundred ninety-six, a taxpayer in any taxable year may elect to contribute to the support of the breast cancer research and education fund. Such contribution shall be in any whole dollar amount and shall not reduce the amount of the state tax owed by such taxpayer. The commissioner shall include space on the corporate income tax return to enable a taxpayer to make such contribution. Notwithstanding any other provision of law, all revenues collected pursuant to this section shall be credited to the breast cancer research and education fund and shall be used only for those purposes enumerated in section ninety-seven-yy of the state finance law.

Article 22 Part 2

§ 627. Gift for breast cancer research and education. Effective for any tax year commencing on or after January first, nineteen hundred ninety-six, an individual in any taxable year may elect to contribute to the breast cancer research and education fund. Such contribution shall be in any whole dollar amount and shall not reduce the amount of state tax owed by such individual. The commissioner shall include space on the personal income tax return to enable a taxpayer to make such contribution. Notwithstanding any other provision of law all revenues collected pursuant to this section shall be credited to the breast cancer research and education fund and used only for those purposes enumerated in section ninety-seven-yy of the state finance law.

APPENDIX V

VEHICLE AND TRAFFIC LAW
Title 4, Article 14

*** § 404-q. Distinctive "drive for the cure" license plates.**

1. Any person residing in this state shall, upon request, be issued a distinctive "drive for the cure" license plate in support of breast, prostate and testicular cancer research bearing the phrase "drive for the cure". Application for said license plate shall be filed with the commissioner in such form and detail as the commissioner shall prescribe.

2. A distinctive "drive for the cure" license plate issued pursuant to this section shall be issued in the same manner as other number plates upon the payment of the regular registration fee prescribed by section four hundred one of this article, provided, however, that an additional annual service charge of twenty-five dollars shall be charged for such plate. Twelve dollars and fifty cents from each twenty-five dollars received as annual service charges under this section shall be deposited to the credit of the breast cancer research and education fund established pursuant to section ninety-seven-yy of the state finance law and shall be used for research and education programs undertaken pursuant to section twenty-four hundred ten of the public health law. Twelve dollars and fifty cents from each twenty-five dollars received as annual service charges under this section shall be deposited to the credit of the prostate and testicular cancer research and education fund established pursuant to section ninety-seven-ccc of the state finance law and shall be used for research and education programs undertaken pursuant to section ninety-seven-ccc of the state finance law. Provided, however that one year after the effective date of this section funds in the amount of six thousand dollars, or so much thereof as may be available, shall be allocated to the department to offset costs associated with the production of such license plates.

APPENDIX VI

STATE OF NEW YORK
HEALTH RESEARCH SCIENCE BOARD
BYLAWS

CHAIRPERSON

The Chairperson of the Health Research Science Board ("Board") shall be designated by the Governor. The Chairperson shall perform the duties ordinarily associated with that office. The Chairperson shall have responsibility for the general supervision of the work of the Board. He or she shall have the power, unless the Board shall have provided for other representation, to represent the Board before the Governor, committees of the Legislature, or other public authorities, and may request any member or members to appear with him or her in his or her stead. The Chairperson shall preside at Board meetings. In the absence of the Chairperson from any meeting, the Board may elect one of its members to preside during such absence.

CODE OF ETHICS

Members of the Board shall comply with Section 74 (Code of Ethics) of the Public Officers Law. No member of the Board should have any interest, financial or otherwise, direct or indirect, or engage in any business, transaction, or professional activity, or incur any obligation of any nature, which is in substantial conflict with the proper discharge of his or her duties as a Board member. Members should exercise their duties and responsibilities as Board members in the public interest of the inhabitants of the State, regardless of their affiliation with, or relationship to, any facility, agency, program, activity, category of provider, or interest group. The principles that should guide the conduct of Board members include, but are not limited to, the following:

a) A Board member should endeavor to pursue a course of conduct that will not raise suspicion among the public that he or she is likely to be engaged in acts that are in violation of his or her trust as a Board member.

b) No Board member should permit his or her employment to impair his or her independence of judgment in the exercise of his or her duties as a Board member.

c) No Board member should disclose confidential information acquired by him or her in the course of his or her duties as a Board member, or by reason of his or her position as a Board member, nor use such information to further his or her personal interests.

d) No Board member should use, or attempt to use, his or her position as a Board member to secure unwarranted privileges or exemptions for himself or herself or others.

e) No Board member should engage in any transaction as a representative or agent of the State with any business entity in which he or she has a direct or indirect financial interest that might reasonably tend to conflict with the proper discharge of his or her duties as a Board member.

f) A Board member should refrain from making personal investments in enterprises which he or she has reason to believe may be directly involved in decisions to be made by him or

her as a Board member or which will otherwise create substantial conflict between his or her duty as a Board member to act in the public interest and his or her private interest.

CONFLICT OF INTEREST

Section 1. Pending Applications and Requests. This section applies both to activities of the full Board and activities of committees of the Board.

a) **Absolute Disqualifications.** When a Board member, or a member of a committee who is not a Board member, submits an application for a grant from the Breast Cancer Research and Education Fund, under Section 2411(1)(e) of the Public Health Law, or a request for access to Pesticide Registry or pesticide application information, under Section 2411(1)(d) of the Public Health Law, or a Board member, or a member of a committee who is not a Board member, or his or her family has an interest, financial or otherwise, whether as owner, officer, director, fiduciary, employee, consultant or supplier of goods or services regarding a facility, agency or program or activity whose application for a grant from the Breast Cancer Research and Education Fund, under Section 2411(1)(e) of the Public Health Law, or whose request for access to Pesticide Registry or pesticide application information, under Section 2411(1)(d) of the Public Health Law, is before the Board or a committee of the Board for consideration or determination, that member shall (i) identify such interest to the Board or committee at any meeting when the application or request is to be considered, (ii) absent himself, or herself, from any portion of any meeting when such application or request is considered, and (iii) not participate in any vote of the Board or committee on such application or request. For purposes of this Article, "family" shall include a spouse, children and any relative living in the member's household.

b) **Disclosure and Possible Disqualification.** When a Board member, or a member of a committee who is not a Board member, or his or her family has (i) any of the above-noted interests in a facility, agency, program or activity, the status of which might reasonably be affected by another facility, agency, program or activity whose grant application or request for access to Pesticide Registry or pesticide application information is before the Board or a committee of the Board, or (ii) when a member has any other interest or association which might reasonably be construed as tending to embarrass the Board or elicit public suspicion that he or she might be engaged in acts in violation of his or her trust as a Board member, he or she shall, at the time of formal consideration of such application or request by the Board or committee, disclose such interest or association so that the Chairperson and, if necessary, the Board or committee can then determine whether his or her participation in the discussion of such application or request or the vote of the Board or committee thereon would be proper.

c) **Procedure.** After a motion is made concerning a grant application or request for access to Pesticide Registry or pesticide application information and prior to discussion or vote, and at the request of the Chairperson, the Board members and members of committees who are not Board members, shall disclose all actual or potential conflicts and, when appropriate, explain the conflicts. In the case of conflicts constituting Absolute Disqualifications, the members with such conflicts shall immediately leave the meeting and remain absent during the period when the application or request is under consideration. In the case of conflicts constituting Possible Disqualifications, the Chairperson shall rule upon such conflicts subject to appeal by motion to the Board or committee that may override the Chairperson's decision by the affirmative vote of a majority of those present, excluding those members who are the subject of the vote.

d) **Compliance with Public Officers Law.** Members of the Board shall comply with Sections 74 and 78 of the Public Officers Law as amended and the following rules governing conflicts of interest: (i) No member shall receive compensation in return for services rendered in relation to matters before any State agency if compensation is contingent upon action or failure to act by such State agency, (ii) no member of the Board who is also associated with any firm or association in which he/she has a specific interest shall sell any goods or services valued in excess of $25 to any State agency unless pursuant to competitive bid, (iii) no member of the Board shall accept any gift (in excess of $75) under circumstances in which it could reasonably be inferred that the gift was intended to influence him/her as a member of the Board, (iv) members of the Board shall avoid any action which might result in or create the appearance of a conflict of interest.

Section 2. Pending Matters-Committees.

a) **Disclosure at Committee Meetings.** When a member of a committee of the Board or his or her family has any of the interests noted in Section 1(a) of this Article in a facility, program or activity the status of which might reasonably be affected by a matter which is before the committee, or when a member has an interest or association which might reasonably be construed as tending to embarrass the Board or committee or elicit public suspicion that he or she might be engaged in acts in violation of his or her trust, he or she shall, at the time of formal consideration of such matter by the committee, disclose such interest or association to the committee so that the committee is fully aware of such member's interest or association. A committee member who discloses such interest or association may, but shall not be required to, abstain from participation in the discussion of or vote on such matter at the committee meeting, unless a member is absolutely disqualified from voting in accordance with Section 1(a) of this Article.

b) **Disclosure at Board Meetings.** When the Chairperson of any committee which considered a matter reports the Committee's deliberations and recommendations to the Board, the Committee Chairperson shall indicate in the report all interests or associations disclosed by the committee members and state how such members voted with respect to the committee's recommendations. A committee member who disclosed such interest or association may, but shall not be required to, abstain from participation in the discussion of or vote on such matter at the Board meeting, unless a member is absolutely disqualified from voting in accordance with Section 1(a) of this Article.

c) **Violation of Provisions.** If any member knowingly and intentionally violates these provisions, the Board or its chairperson shall refer the matter to the Commissioner of Health for appropriate action.

DESIGNATION AND DUTIES OF THE SECRETARY

The Board shall request the Department of Health to designate a Department employee as the Board's Secretary.

The Secretary shall prepare and send official notices of actions of the Board and shall administer the daily business of the Board under the general direction of the Chairperson. The Secretary shall send a copy of the Minutes of each meeting of the Board to each member of the Board as soon as practicable after the meeting. The Minutes, as approved or corrected, shall

serve as the official record of a meeting of the Board. Minutes shall be distributed or made available to the public after they have been approved by the Board. The Secretary shall make available records requested under the Freedom of Information Law and make announcements to the media and public of scheduled meetings as required by the Open Meetings Law.

MEETINGS OF THE BOARD

a) The regular meetings of the Board shall be held at least six times during the first year subsequent to December 1, 1997, and at least four times a year thereafter at a date, time and place approved by a majority of members, unless otherwise determined by the Board or by the Chairperson, who shall notify the Secretary at least ten business days in advance of the meeting. Special meetings of the Board may be called by the Chairperson at his or her discretion, or on the request of two members, and shall be called by the Chairperson on the written request of three members.

b) At least one meeting each year shall be a public hearing at which the general public may question and present information and comments to the Board with respect to the operation of the Board, the Breast Cancer Research and Education Fund, the Prostate and Testicular Cancer Research and Education Fund and pesticide reporting established pursuant to Sections 33-1205 and 33-1207 of the Environmental Conservation Law. At the public hearing, the Commissioner of the Department of Environmental Conservation or his or her designee shall make a report to the Board with respect to the efficiency and utility of pesticide reporting established pursuant to Sections 33-1205 and 33-1207 of the Environmental Conservation Law.

c) At least some portion of every regular Board meeting shall be set aside for public comment. A portion of one Board meeting each year shall be set aside for presentations of progress reports from selected award winners.

d) 1) The Secretary shall notify each Board member of Board meetings and shall send an agenda to his or her usual address not less than ten business days before the meeting.

2) A majority of the voting members of the Board shall constitute a quorum for the transaction of any business or the exercise of any power or function of the Board and all matters requiring action shall be passed by a vote of a majority of the voting members of the Board. (A voting member abstaining from a vote shall be counted as present for the purpose of establishing a quorum.) Except as provided below, all meetings shall be conducted in accordance with Robert's Rules of Order Newly Revised, and a record of each vote shall be maintained. Non-voting *ex-officio* members of the Board may make motions to be considered by the Board, but may not vote on these or any other motions before the Board. The normal method of voting shall be by roll call. A roll call vote on any question shall be taken by ayes and noes, abstentions noted, and a record of how each member voted entered in the Minutes.

3) Any member who fails to attend three consecutive meetings of the Board, unless excused by formal vote of the Board, shall be deemed to have vacated his or her position.

4) Meetings of the Board shall be noticed and conducted in accordance with the requirements of Article 7 (Open Meetings Law) of the Public Officers Law. Such

meetings shall be open to the public except when otherwise provided by law. Guidelines for observers shall be adopted by the Board.

ORDER OF BUSINESS

The order of business may be altered at the Chairperson's discretion or upon the request of a Board member.

A portion of each Board meeting shall be set aside for the development of an agenda for the next Board meeting.

PROPOSAL REVIEW PROCESS

Ad Hoc Review Panels

There shall be one or more independent scientific review panels to review proposals (referred to as "applications for grants" in Public Health Law § 2411(1)(e))for merit and to make recommendations to the Board for funding

DOH staff, on behalf of the Board, will establish one or more independent scientific review panels, each of which shall be composed of at least one breast cancer survivor and/or activist, and one expert in breast cancer research and/or education. The number of independent scientific review panels will be dependent on the number of proposals received by the Board.

Responsibilities of the Board

The Board shall consider and rank proposals considered by the independent scientific review panels. Following an affirmative vote of Board members, the Board shall recommend that the Commissioner of Health approve those proposals for which the Board determines that funding is available. Board or committee meetings, or portions thereof, at which Board or committee members consider, rank, discuss or vote on proposals received by the Board may be conducted in executive session as authorized by the Open Meetings Law.

Summary Report

A summary report of the proposal review process will be prepared by Department of Health staff in consultation with the Board and made available to the public subsequent to the Board's recommendations to the Commissioner of Health.

Guidelines

The Board shall adopt guidelines that will specify additional aspects of the proposal review process.

COMMITTEES

There shall be the following Standing Committees:

1. On oversight of the development of requests for proposals (grant applications), and the process used to review proposals received by the Board; and on evaluating breast/prostate/testicular cancer research and educational program effectiveness nationwide and recommending future breast/prostate/testicular cancer research projects, called the:

   Committee on Research Needs and Education Program Effectiveness

2. On oversight and management of information requested by researchers from the New York State Department of Environmental Conservation Pesticide Sales and Use Registry and from private pesticide applicators, called the:

   Committee on Access to Pesticide Registry and Pesticide Application Information

3. On Breast Cancer Research and Education Fund contributions, and the Board's outreach activities, called the:

   Committee on Funding and Outreach

Each Standing Committee shall consist of one or more members of the Board and may include non-Board members. The Chairperson of the Board shall appoint all Standing Committees and designate their Chairpersons. Duties of Standing Committees shall be prescribed by the Chairperson of the Board with approval by a majority of Board members.

In appointing Board members to any Standing Committee, the Chair shall, to the extent practicable, ensure that the Committee's composition reflects the overall composition of the Board and that any such Committee includes Board members and, if appropriate, non-Board members with relevant interests.

The Board may, at any time, provide for the appointment of a special committee on any subject. All such special committees not previously discharged by the Board shall be considered discharged one year following their appointment, unless the Board shall move to continue them.

A majority of the persons appointed to serve on a committee shall, if at least one Board member is present, constitute a quorum for the committee.

All committee matters requiring action or a formal recommendation shall be passed by a vote of a majority of the members appointed to serve on the committee.

When making a report to the Board, a committee should, in addition to reporting any recommendations of the majority of the committee, summarize any significant deliberations leading to such recommendations as well as opinions or recommendations of committee members who did not support the majority recommendations.

OFFICE OF THE BOARD

The official headquarters of the Board (at which the official copies of its Minutes, records, documents and other papers shall be kept) shall be at the offices of the Commissioner of Health at Albany, New York. The Secretary shall be responsible for the safe-keeping of all Minutes, records, documents, correspondence and other items belonging to the Board. Every member of the Board and any other person duly authorized by a member shall have access at all times during the ordinary office hours of the Department of Health to all such Minutes, records, documents, correspondence and other items belonging to the Board; provided, however, that persons authorized by members shall not have access to records, documents, correspondence or other items that are exempt from disclosure or confidential under the Freedom of Information Law, the Personal Privacy Protection Law, or any other state or federal law. The Secretary shall designate some person to be in charge of all such Minutes, records, documents, correspondence and other items belonging to the Board during his or her absence from the office.

AMENDMENT OF BYLAWS

These Bylaws may be amended by the affirmative vote of the majority of the voting members of the Board at any regular or special meeting, provided that notice of the proposed amendment has been given at a prior meeting and that a copy of the proposed amendment has been sent by the Secretary to each member of the Board at least ten business days prior to the vote.

APPENDIX VII

2006-2008 BREAST CANCER RESEARCH POSTDOCTORAL FELLOWSHIP AWARD RECIPIENTS AND GRANTING ACTIVITIES

Previously unreported highlights of research accomplishments related to 29 Health Research Science Board (HRSB) grant contracts follow:

Michael A. Bachelor, Ph.D./Zhi-Jian Liu, M.D., Ph.D., Columbia University College of Physicians and Surgeons, "Novel Vector to Promote Radiosensitivity and Apoptosis in Breast Cancer Cells," Paul B. Fisher, M.Ph., Ph.D., mentor. $120,000, contract number C020906, January 1, 2006 – December 31, 2007.

Barriers to effective gene therapy, particularly for the treatment of cancer, include potency and specificity. This research aims at improving the efficacy of gene therapy through two strategies, namely, combination gene therapy with irradiation and construction of a new and enhanced therapeutic virus that simultaneously expresses two cancer-specific therapeutic genes (a bipartite virus).

A complete set of therapeutic adenoviruses expressing *mda*-7/IL-24 (Ad.*mda*-7), TRAIL (Ad.TRAIL) or both *mda*-7/IL-24 and TRAIL (Ad.bipartite) under the control of cytomegalovirus (CMV) promoter was successfully constructed. The protein levels of MDA-7/IL-24 and TRAIL in human breast cancer cells were analyzed following infection of these viruses in human breast cancer cells. A similar level of expressed protein was detected when identical plaque formation units (pfu) of these viruses were applied to human breast cancer cells.

The ability of these therapeutic viruses to inhibit tumor cell growth and induce apoptosis *in vitro* was analyzed in a panel of human breast cancer cells, i.e., MCF-7, T47D, MDA-MB-231 and MDA-MB-453 cells. Despite a huge difference in the level of membrane Coxsackie-adenovirus (CAR) receptors in these cell lines, all of these therapeutic viruses showed growth-inhibitory effects in MTT assays [the colorimetric assays that measure the reduction of a tetrazolium component (MTT) into an insoluble formazan product] and apoptosis-inducing effects in Annexin V binding assays. An enhanced biological effect was observed in human breast cancer cells infected with Ad.bipartite therapeutic viruses, compared to those infected with either Ad.*mda*-7 or Ad.TRAIL. This result suggested a cooperative effect of MDA-7/IL-24 and TRAIL protein when expressed by a bipartite therapeutic virus. Experiments are in progress to define the underlying mechanism of this cooperative effect. The combinational effect of irradiation with these newly developed therapeutic viruses is also being explored. Studies to date show very promising results, i.e., irradiation enhances the *in vitro* anti-tumor efficacy of these therapeutic viruses in human breast cancer cells.

A mouse model containing human breast cancer orthotopic xenografts on each flank will be investigated to analyze *in vivo* effects of these therapeutic viruses, as well as potential combinational effects of irradiation with the viruses. By establishing tumors on each flank of the animal, and treating tumors only on one side of the animal with the therapeutic virus and/or irradiation, it will be possible to evaluate potential "bystander" anti-tumor effects of both MDA-7/IL-24 and TRAIL in inhibiting both the primary and distant tumors.

Merav Ben-Yehoyada, Ph.D., Columbia University Medical Center, "Function of BRCA1 in the Maintenance of DNA Replication Fork Integrity," Jean Gautier, Ph.D., mentor. $120,000, contract number C020907, January 1, 2006 – December 31, 2007.

The DNA molecule carries the genetic information necessary for a cell to grow and develop normally. This information must replicate faithfully before cell division, in order to be transmitted to the daughter cells. However, the DNA is constantly subjected to damaging events of external or physiological origins. Occurrence of DNA damage alters the genomic sequence and leads to cancer development. To control genomic instability, cells have evolved mechanisms preventing cell division in the presence of DNA damage and promoting DNA repair.

The BRCA1 protein has been implicated in various cellular processes, including DNA repair, transcriptional regulation, chromatin remodeling and cell-cycle checkpoint regulation. BRCA1 forms a functional complex with BARD1, which is required for their proper localization, E3 ligase activity, DNA binding and protein stability. Either BRCA1 or BARD1 depletion leads to early embryonic lethality in mice and genomic instability *in-vitro* and *in-vivo*. In addition, BRCA1/BARD1-deficient cells are hypersensitive to crosslinking agents such as cisplatin and mitomycin C, and double-strand breaks formation. Indeed, BRCA1 is essential for initiation of homologous recombination (HR), repair of double-strand breaks and for facilitating HR bypass of stalled replication forks.

Using a Xenopus cell-free system, the role of BRCA1/BARD1 complex at the replication fork was investigated. Specifically, their role in the repair and checkpoint induction following replication of interstrand crosslink (ICL) DNA damage was studied. Investigations addressing the repair of ICLs have been very limited, mostly due to the heterogeneous nature of the lesions arising from crosslinking agents. In order to overcome this obstacle, a plasmid DNA containing a single defined ICL was generated. The crosslinked plasmid is replicated and repaired in Xenopus cell-free extract, therefore making this system ideal to study the role of BRCA1/BARD1 complex in the ICL repair process. In addition, the ICL plasmid induces DNA damage checkpoint following its replication as compared to a control plasmid, enabling study of the signaling events following formation of a stalled/collapsed replication fork. The research showed that the BRCA1/BARD1 complex may participate in the signaling pathway from ICL DNA damage. In this system, the role of BRCA1/BARD1 at the replication fork can be specifically addressed, and new rational bases for innovative therapeutics to treat breast cancer may be uncovered.

Ryosuke Hayami, Ph.D., Columbia University College of Physicians and Surgeons, "Animal Models for Snail's Role in Breast Cancer Development," Thomas Ludwig, Ph.D., mentor. $108,124, contract number C020909, January 1, 2006 – December 31, 2007.

Loss of Ecadherin (the molecular glue) from primary tumors is the hallmark of onset of epithelial-to-mesenchymal transition (EMT) and signals the beginning of metastisis (invasive tumor growth).

Recently, Snail protein was discovered to be a molecular switch that turns off E-cadherin production to jump-start the EMT process. It was found that invasive human breast tumors produced high levels of Snail protein, but very low or no E-cadherin. In contrast, non-invasive tumors showed low levels of Snail protein and maintained E-cadherin. These discoveries suggest that abnormal production of Snail may be connected with breast cancer development and conversion of primary breast tumors into invasive metastasis.

This project tests that hypothesis and whether suppressing the production of Snail protein slows down progression of breast tumors into invasive metastasis or prevents breast cancer development.

A strain of mice genetically modified to overexpress Snail protein in the mammary gland and another that specifically lacks Snail protein expresssion in the breast have been generated. These animals are being monitored for any sign of mammary tumor development. An antibody that specifically recognizes Snail protein has been developed. This antibody is a valuable tool for analyzing Snail expression in animal models of breast cancer.

These animal models could become a model system to test new therapies that specifically prevent primary tumors from becoming invasive. The efficacy of the therapies in this model system could be predictive of their potential to prolong the lives of breast cancer patients.

Wen Hong Shen, Ph.D., Columbia University College of Physicians and Surgeons, "Role of PTEN in Mediating Indomethacin Anti-Cancer Activity," Yuxin Yin, M.D., Ph.D., mentor. $120,000, contract number C020910, January 1, 2006 – December 31, 2007.

Indomethacin has been reported to induce cancer cell death and reduce risk of breast cancer, and may rely on the expression of an important tumor suppressor, PTEN, one of the most mutated genes in human cancers. Data from this study indicate that cancer cells with high levels of wild-type PTEN are killed more easily by indomethacin, whereas lack of PTEN or PTEN mutation confers indomethacin resistance. Therefore, this project exploits the mechanism by which PTEN mediates indomethacin-caused breast cancer cell death. The data should increase the understanding of indomethacin antitumor properties, and the role of PTEN and its potential targets in mediating indomethacin-induced breast cancer cell apoptosis.

The research demonstrates that PTEN induces MKP-2 and suppresses ERK1/2 activity, which mediates cancer cell death in response to oxidative stress and indomethacin as a chemotherapeutic agent. It was determined that cancer cells with high levels of PTEN are more sensitive to indomethacin-induced cell death, whereas PTEN mutations lead to indomethacin resistance. Indomethacin reduces the activation of ERK1/2, whereas ectopic induction of both PTEN and MKP-2 in breast cancer cells leads to greater suppression of the ERK signaling pathway. The study reveals that PTEN induces MKP-2 by acting on chromatin and physically interacting with the MKP-2 promoter. Interestingly, breast cancer cells became super-sensitive to indomethacin when MKP-2 is overexpressed, suggesting that MKP-2 acts as a potent cell death mediator in response to indomethacin treatment.

This research project established a molecular link between PTEN and the mitogen-activated protein (MAP) kinase-signaling pathway, an important oncogenic pathway known to promote cancer cell survival and growth. The data demonstrate how PTEN mediates cellular apoptotic response to indomethacin administration for patients with breast cancer and offers a solid background for further development of better strategies in breast cancer treatment.

Anne Marie Doody, Ph.D., Cornell University, "RNAi: A Therapeutic Approach for Treatment of Breast Cancer," David A. Putman, Ph.D., mentor. $120,000, contract number C020911, January 1, 2006 – June 30, 2008.

The RNAi pathway holds great potential for use as a therapeutic strategy in treatment of genetic diseases, including breast cancer. Viral vectors have shown the greatest success in interrupting

this pathway, but many concerns have been raised about their immunogenicity. For this reason, polymeric vectors which mimic the action of viral vectors are being developed. These vectors, however, are relatively inefficient in comparison to viral vectors and require improvement to become a viable therapeutic agent.

Two polymeric vectors were chosen for this study that was designed to evaluate their efficacy using *in-vitro* model systems and to determine the structural characteristics of these polymers that relate to nucleic acid delivery.

Specifically, libraries of PLL-Imidazole, 25,000 branched PEIb-lipid, and 25,000 branched PEIb-carbohydrate conjugates were synthesized and characterized. Biophysical characterization, cytotoxicities, and *in-vitro* transfection efficiencies were determined with nanocomplexes formed using these libraries at varying weight-to-weight (w:w) ratios, and siRNA or plasmid DNA concentrations. The HR5-CL11, HepG2, and MDA-MB-231 cell lines stably expressing luciferase were used as model systems *in vitro*. Successful siRNA and plasmid DNA delivery was observed with the low- and mid-molecular weight PLL-Imidazole, 25000 PEIb-lipid, and 25,000 PEIb-carbohydrate conjugates within a range of w:w ratios and siRNA concentrations. In the case of the PEIb-carbohydrate polymers, this success was cell-line dependent.

Thus, the ability of these polymeric vectors to transfer functionally active siRNA to cells in culture is surprisingly dependent on the siRNA's biophysical and structural characteristics, when compared to their relative success and ease of use for DNA delivery.

These limited libraries and corresponding structure/function analysis form the foundation upon which larger, more comprehensive polycationic libraries can be designed and evaluated to understand further how polycation transfection reagents function. Doing so will generate data on new means to deliver chemotherapeutic agents effectively to treat breast cancer.

Tong Zhang, Ph.D., Cornell University, "Regulation of Breast Cancer-Related Nuclear Factors by NAD+," William Lee Krauss, Ph.D., mentor. $120,000, contract number C020912, January 1, 2006 – December 31, 2007.

Two enzymes in breast cancer cells generate a factor, NAD^+, that is used by two other enzymes in the nucleus of these cells to modify protein in the cells. This protein modification is associated with the cells' response to stress, survival and to metabolism. Also, the activity of the receptor that binds estrogen in the cells is modified, which may play a critical role in breast cancer.

The study's goals were to determine how the NAD^+-generating proteins control the function of the two enzymes in the nuclei of breast cancer cells and how these enzymes in turn control the estrogen receptor function.

The completed studies have proved that the NAD^+ -generating enzymes do perform that function in breast cancer cells and that these two enzymes do control the activities of many genes through interaction of the two nuclear enzymes. Future studies will focus on the role of the NAD^+-generating enzymes in controlling the function of estrogen receptor activity and thus breast cancer cell function.

Luca Busino, Ph.D., New York University School of Medicine, "In Search for the Ubiquitin Ligase of Cycline D1, a Key Oncoprotein in Breast Cancer," Michele Pagano, M.D., mentor. $120,000, contract number C020913, January 1, 2006 – December 31, 2007.

Previous studies have revealed an elevated breast cancer risk in women night workers associated with occupational exposure to light at night. This study seeks to determine the molecular pathway that forms the basis of this observation.

This work has identified an enzyme that is a key controlling element of the circadian clock that controls aspects of the growth of cells. Results from this and other research have also revealed that a certain protein, and the gene associated with it, are absent or significantly reduced in human breast tumors, as compared to normal tissue. This project has confirmed that the protein that is reduced in breast tumors destabilizes another group of proteins. These proteins become more stable when the levels of the destabilizing protein are reduced, as occurs in breast tumors. This stabilization of the protein group prevents proper oscillations of the circadian clock. Further research is being conducted to determine whether the observed effects play a role in the breast cancer risk of women night workers.

Silvia Canudas, Ph.D., New York University School of Medicine, "Tankyrase 1 and Telomere Function in Breast Cancer and Normal Cells," Susan Smith, Ph.D., mentor. $120,000, contract number C020914, January 1, 2006 – December 31, 2007.

Telomeres are long strands of DNA that form at the ends of chromosomes. They are protected by bound proteins because their integrity is essential for cell growth, and their length plays a role in aging and cancer. It has been proposed that when cells undergo extended reproduction they lose telomere function in a process that corresponds with the development of breast cancer. Telomere length is controlled by an enzyme, tankyrase 1, and when its activity is blocked, telomere shortening results. Since tankyrase 1 is found in significantly higher concentrations in breast tumors than in the surrounding healthy tissue, it may be a good target for anti-cancer therapies.

The aim of these studies is to determine the basis for the association of telomere length with breast cancer.

Adam Mor, Ph.D./Brian D. Onken, Ph.D., New York University School of Medicine, "Characterization of Isoprenylcysteine Carboxylmethyltransferase," Mark Philips, M.D., mentor. $120,000, contract number C020915, January 1, 2006 – December 31, 2008.

Breast cancer, which involves the uncontrolled growth of cells, can result from abnormal control of a variety of genes. The best-studied gene implicated in supporting cancer development is the *Ras* gene, which directs the formation of the Ras protein. This protein can act as a cellular switch, and when a mutated form of the protein remains switched on, cancer can result. For Ras protein to function as a switch, it must be associated with the covering or membrane of cells. Another protein, isoprenylcysteine carboxymethyltransferase (Icmt), participates in Ras protein's association with the cell membrane, and can control Ras protein's function by modifying its structure. Icmt is thus a target for anti-cancer drugs.

This project aims to develop an understanding of Icmt function and its structure in cellular membranes. It is believed that certain elements or forms of the Icmt structure are required for it to function. To test this hypothesis, more than 25 modified forms of Icmt have been prepared

for this study. Only one of these modified forms of Icmt showed greater than 90 percent loss of activity. Other variant forms exhibited activity changes that were less marked. Initial hopes that several modified structures of Icmt would be formed, thus revealing all of the structure of Icmt necessary for its activity, were thus not realized.

An alternative approach has been developed using a form of RNA that blocks the ability of the Icmt gene to act as a template for the formation of Icmt proteins. A new method to probe the structure of Icmt has been devised, and initial results obtained. Additional studies will be undertaken to help in the discovery of drugs to inhibit Icmt and thus prevent Ras protein from binding cell membranes.

Laurent Pascual-Le Tallec, Ph.D./Ryo Koyama-Nasu, Ph.D., New York University School of Medicine, "Chromatin Remodeling in Breast Cancer," Naoko Tanese, Ph.D., mentor. $120,000, contract number C020916, January 1, 2006 – December 31, 2007.

Every cell in the human body contains the identical genome, but each cell type uses the information available in the genome in a way that is unique to that cell type. The proteins produced from the information in the genome provide a unique identity to each cell type. Selection of the proteins for formation is based on the messenger RNAs synthesized in the various cell types. The selection process is controlled by proteins called transcription factors, which act by binding to selected DNA sites.

The DNA is highly compacted in the nucleus of the cell, resulting in chromatin fibers. The transcription factors to detect target sites in the genome must contend with chromatins, which are naturally inhibitory to factor binding. Transcription factors can only bind to the DNA if the chromatin structure is altered, which is carried out by multi-protein complexes. This is particularly the case with genes that control cell growth and could play a role in cancer development.

One subunit of these protein complexes, Osa, has been found in these studies to bind to histones, which make up chromatin. Such binding could help target specific genes, including estrogen-receptor responsive genes, in the DNA for the ultimate synthesis of specific proteins. Research here has identified the site on Osa that binds to the histones. Future studies will focus on how binding of Osa to histones affects the synthesis of specific proteins using specific genes as templates.

Deborah Silvera, Ph.D., New York University School of Medicine, "Translational Control in Inflammatory Breast Cancer Progression," Robert J. Schneider, Ph.D., mentor. $120,000, contract number C020917, January 1, 2006 – December 31, 2008.

Inflammatory breast cancer (IBC) is a highly aggressive form of breast cancer. Although its incidence is low (one to six percent of breast cancers in the United States), it is associated with a low survival rate. Little is known about the molecular basis for the development of IBC, but it has been reported that the tumors are highly adapted to hypoxia and are very effective in inducing vascularization. There is no report addressing the role of and important regulatory step in cell growth, control of initiation of protein synthesis (or "translation"), in the development of IBC.

The aim of this project is to elucidate the role that protein synthesis regulation plays in the development of IBC. In particular, protein synthesis initiation factors implicated in the

development of other cancers, as well as factors involved in signaling to the protein synthesis machinery, those of the PI3K/mTOR pathway, are being investigated. The system used to investigate the regulation of translation is based on cells derived from IBC patients, combined with analysis of factors of interest in patient tissue samples. Once likely candidates are identified, genetic changes are introduced into IBC cells to impair their expression. These modified cells are then utilized to study the effect of these factors on tumor growth using animal models.

By examining the IBC cells and analyzing patient tissue samples, it has been determined that eIF4G, a protein synthesis initiation factor, is overexpressed in IBC. To examine whether eIF4G is involved in tumorigenesis, researchers genetically impaired its production in IBC cells and studied the effect of this alteration on tumor growth in mice and chick animal models. The investigators found that eIF4G ablation leads to a marked reduction of tumor growth in both systems. This defect is accompanied by a decrease in the production of molecules that play a key role in induction of vacularization required for the tumor to survive, as well as reduction in their levels, and aberrant cellular localization of proteins shown previously to be molecular markers of IBC. Examination of the signaling molecules in the PI3K/mTOR pathway of IBC cells revealed that the pathway is activated, but genetic modification of these factors has not yet revealed a significant effect on tumor growth or adaptation to hypoxia.

Future directions of this project include elucidation of the mechanism of eIF4G's role in IBC tumor growth, including the mechanism whereby eIF4G is required to maintain appropriate levels of molecular markers of IBC. Identification of key players in development of IBC will be a gateway to single out targets for future treatment strategies.

Chi-Chen Hong, Ph.D., Roswell Park Cancer Institute, "Determinants of Weight Gain in Women With Early Stage Breast Cancer," Christine Ambrosone, Ph.D., mentor. $120,000, contract number C020918, January 1, 2006 – December 31, 2008.

Weight gain is common in early-stage breast cancer patients receiving adjuvant chemotherapy, and has been associated with poorer prognosis. Weight gain may be, in part, due to treatment-related reductions in ovarian function, including treatment-induced amenorrhea. Investigators have hypothesized that women with the largest declines in sex hormone levels should gain the most weight, and that this relationship would be modified by genetic factors, lifestyle and psychosocial factors. The goals of the study are to examine weight gain and treatment-induced menopause in relation to treatment-related changes in sex hormone levels, and in relation to genetic polymorphisms in sex hormone pathways.

A prospective longitudinal study of weight gain is being conducted in 200 patients, aged 35 to 75 years, with non-metastatic breast cancer. After informed consent, serial biospecimens and survey data are collected to measure hormone levels and genetic polymorphisms, and to assess menopausal status, anthropometry, diet, physical activity, and psychological variables at baseline, six and 12 months. These factors will be evaluated in relation to weight changes during and following therapy.

Recruitment of participants was initiated in January 2007. As of this writing, 226 participants have been enrolled. From this group, 31 individuals withdrew, and five were lost to followup, leaving 190 active participants. Of a possible 145 women, 123 have had a six-month followup visit (85 percent), and 92 of a possible 107 (86 percent), a one-year followup visit; 93 percent of these participants provided at least one followup blood sample. Within the last year, researchers developed a supplementary questionnaire to collect information on temperature

perception, and use of vitamin supplements, herbals and other compounds, after breast cancer diagnosis. As a result, the study databases were recently updated to allow double entry of these data, and the backlogged data collected with the supplementary questionnaire are being entered. To increase the rate of enrollment, beginning on October 31, 2007, the eligibility criteria for the study protocol was broadened to women 18 years of age and older.

To augment study enrollment, potential collaborators in Philadelphia are sought to expand the study to the Hospital of the University of Pennsylvania, which treats approximately 700 breast cancer patients per year. Once follow-up is completed for all participants, it is expected that the study findings will show a relationship between declines in sex hormone levels and weight gain in newly diagnosed breast cancer patients, and will provide information on how lifestyle and psychosocial factors impact or modify this weight gain.

These findings will help identify women who are most susceptible to weight gain after diagnosis with breast cancer, based on biologic characteristics, as well as modifiable factors. From a public health viewpoint, findings from this study may reveal strategies to improve women's health after breast cancer and optimize their long-term survival.

Bin Wu, Ph.D./Gong Chen, Ph.D., Memorial Sloan-Kettering Cancer Center, "Chemical Synthesis of Erythropoietin," Samuel J. Danishefsky, Ph.D., mentor. $120,000, contract number C020919, January 1, 2006 – December 31, 2007.

Erythropoietin (EPO) is a glycoprotein hormone that has become a leading therapeutic for the treatment of cancer-related anemia. Despite the clear-cut clinical importance of this compound, attempts to evaluate rigorously the role of glycosylation on the activity and stability of EPO have thus far been complicated by the daunting difficulties associated with isolating significant quantities of homogenous EPO. Total chemical synthesis provides a unique opportunity to meet this challenge. The goal of this project is therefore to prepare synthetic homogeneous EPO and gain access to a range of EPO analogues for structure-activity relationship investigation. Broadly speaking, an undertaking of this magnitude could well lead to the development of strategies and protocols generally useful to the entire field of glycoprotein synthesis.

The synthesis of the fucosylated biantennary N-linked glycan and O-linked glycophorin, two essential carbohydrate components of EPO, was achieved. Since synthesis of the glycans has been addressed, assembly of glycopeptides is planned. A maximally convergent route to EPO would involve preparation of the four different glycopeptide fragments, to be subsequently joined through some form of ligation to furnish the fully glycosylated protein backbone. Development of a repertoire of ligation methods could well be critical to the success of the project. In considering a strategy for *de-novo* synthesis of EPO, the paucity of cysteine residues on the molecules was noted. Cysteine-free peptide-bond-forming protocols were devised in the broad context of a phenolic ester strategy. While this method has enabled completion of the EPO 114–166 domain and the EPO 22–37 domain, it requires initial installation of an auxiliary, which must subsequently be cleaved. In practice, the auxiliary-based approach may suffer from significant practical limitations. To circumvent the issue of auxiliary removal, another major effort to pursue a direct auxiliary-free coupling strategy for glycopeptide synthesis was initiated. This effort led to successful development of two sets of powerful methods for accomplishing cysteine-free glycopeptide ligation. The fragment-coupling possibilities, previously restricted to cysteine-based and auxiliary-based, non-cysteine ligation, have now been expanded in

important ways. In particular, the metal (AgCl) and metal-free (TCEP)-mediated acyl donor enhancement of a recently developed C-terminal ester resulted in a major expansion of options in pursuit of the total chemical synthesis of EPO.

Amy E. Millen, Ph.D., University at Buffalo, "Vitamin D and Breast Cancer: An Epidemiologic Approach," Jo L. Freudenheim, M.S., Ph.D., mentor. $119,998, contract number C020920, January 1, 2006 – December 31, 2007.

This research investigates: 1) the association between risk of incident breast cancer in an observational cohort study and proxy measures of vitamin D exposure (baseline solar irradiance, and region of residence at baseline, birth, age 15 and age 35); and 2) the association between risk of breast cancer and genetic variation in the vitamin D receptor (VDR) in a case-control study.

Analyses in the Women's Health Initiative Study (WHI)
Data to conduct these analyses were made available in October 2006 through the WHI Clinical Coordinating Center in Seattle, Washington. This project was on hold until the WHI clinical trials data were published and analyses were completed for other WHI projects. Analyses of relationships between incident breast cancer risk and proxy measures of vitamin D exposure are completed.

Analyses in the Western New York Exposures in Breast Cancer (WEB) Study
The genotyping for the VDR single nucleotide polymorphisms (SNPS), Fok1 and Cdx2, has been completed. Data analysis on the association between breast cancer risk and these two VDR SNPS genotypes is completed. An investigation of associations between dietary and supplemental intake of vitamin D and risk of breast cancer has begun. Analyses comparing breast cancer risk and major lifetime occupation are underway. Data on lifetime occupation are being refined and entered to create a dataset.

These studies will provide preliminary data for future investigations on relationships between vitamin D and breast cancer risk. There is significant vitamin D insufficiency and deficiency throughout the world, with a potential major impact on public health. This research will add more knowledge to the body of evidence for a relationship between vitamin D status and breast cancer.

Kun Cai, Ph.D./Chunyang Zheng, Ph.D., Weill Medical College of Cornell University, "The Role of the Transcription Factor Rex1 in Human Breast Cancer," Lorraine J. Gudas, Ph.D., mentor. $120,000, contract number C020921, January 1, 2006 – December 31, 2007.

Retinoids, which include vitamin A (retinol) and its natural and synthetic derivatives, are very important for many biological processes, and well-known as promising drugs to prevent and treat various cancers. The use of ATRA (all-trans retinoic acid) to treat acute promyelocytic leukemia (APL) is one successful example, suggesting that retinoids can serve as drugs to treat human breast cancer.

Aberrant vitamin A metabolism may promote the development of various cancers. The normal human breast takes up vitamin A and stores it as esters. An enzyme, LRAT, catalyzes formation of the esters. The level of LRAT is high in normal human breast, but very low in breast cancer cells. This study addresses the hypothesis that human breast cancer cells lack

LRAT, which leads to a local retinoid deficiency in the tumor, and that restoration of LRAT will result in an increase of retinol storage, in turn possibly suppressing tumor progression.

The goals of this project are to define the molecular mechanisms that result in low levels of LRAT in breast cancer, and to devise new therapeutic approaches to restore LRAT and inhibit tumor growth.

Preliminary results indicate that LRAT mRNA levels in the human breast cancer MDA-MB-231 cells are lower than those in cultured normal human breast epithelial cells (HMEC). Other studies identified Rex-1 and Oct-4 as potential markers of human embryonic and adult stem cells, and Rex-1 and Oct-4 expression was observed in normal renal parenchymal tissue and renal tumor. However, reverse transcriptase-polymerase chain reaction (RT-PCR) analysis did not detect any Rex-1 and Oct-4 expression in HMEC and MDA-MB-231 cells. The luciferase activity of a 2.3 kb LRAT promoter in MDA-MB-231 cells was found to be lower than that in HMECs, indicating that various transcription factors are present at different levels on this promoter in the normal as compared to the cancer cells. Luciferase assays also indicated that the LRAT promoter sequence harbors *cis* elements required for RA responsiveness in HMEC. A real-time quantitative RT-PCR assay showed that STRA6 expression in MDA-MB-231 cells is not defective compared to HMEC.

These experiments show that the LRAT promoter is able to respond to retinoic acid and retinol treatments in normal cells, and differences in various transcription factors might explain the loss of LRAT in breast cancer.

Christian Riebeling, Ph.D., Albert Einstein College of Medicine of Yeshiva University, "Fragmentation of the Golgi Apparatus in Breast Cancer Cells," Dennis Shields, Ph.D., mentor. $120,000, contract number C021327, January 1, 2006 – December 31, 2007.

Cancer cells proliferate rapidly and in an uncontrolled fashion, although there is usually damage to the cellular DNA. This rapid growth contrasts with normal cells. Normally, in response to DNA, damaged cells undergo programmed cell death termed "apoptosis," a process that effectively eliminates potentially cancerous cells from an organ. Consequently, a major objective in breast cancer research and for many tumors is to understand how cancer cells evade apoptosis and sometimes proliferate even following treatment with anti-cancer therapies. This research focuses on how two classes of enzymes, which generate so-called "signaling lipids," participate in the mechanism that allows cancer cells to escape the death pathway. Phospholipase D (PLD) generates phosphatidic acid (PA), which has been implicated in regulating many cellular processes, including growth, proliferation and cell division. Furthermore, several studies have shown that elevated levels of PLDs are present in breast carcinomas, suggesting that increased PA production contributes to tumor growth and survival. PA also stimulates the enzymatic activity of the second class of enzymes, phosphatidylinositol 4-phosphate 5-kinase (PIP5K), thus generating phosphatidylinositol 4,5-bisphosphate (PIP2). PIP2 is well-known for its role in receptor-stimulated signaling, but is also required for PLD activity and is itself an inhibitor of the apoptotic machinery.

A cell-free system was used to synthesize PLD, and an analysis performed on how it is cleaved during apoptotic cell death and Golgi fragmentation. One of the PLDs, PLD1, was rapidly digested, whereas another form, PLD2, was relatively resistant. Conditions were established to allow measurement of the enzymatic activity of the PLDs following their cleavage. Strikingly, the activity of PLD1 was not lost after cleavage by caspases, enzymes that mediate the cell death pathway; instead, its response to several regulatory stimuli was altered. Using

recombinant DNA technology and site-directed mutagenesis, three specific sites of enzyme digestion were identified and correlated with observed changes in response to regulatory stimuli. One of the cleavage sites lies within a region of the enzyme that has not been shown previously to be involved in regulation of its activity. In a similar approach, PI4P5Ks were found to have no protective role in breast cancer cells.

Most importantly, despite their proteolytic cleavage in response to apoptosis-inducing drugs, both forms of PLD retained their enzymatic activity and generated their product; thus, the data explain how high levels of the enzymes in tumor cells are able to promote growth and survival even in response to drugs that would be expected to kill such cells.

Suwen Wei, M.D., Ph.D., Albert Einstein College of Medicine of Yeshiva University, "CSF-1 Signaling in Mammary Tumor Progression and Metastasis," E. Richard Stanley, Ph.D., mentor. $120,000, contract number C021328, January 1, 2006 – December 31, 2007.

Breast cancers are comprised not only of tumor cells but also of white blood cells. The macrophage is one kind of white blood cell containing enzymes that ingest and destroy bacteria and other microorganisms to combat infection. Recent studies indicate that macrophages in tumors can have negative effects on tumor progression. Thus, understanding the regulation of tumor-associated macrophages (TAMs) should yield an opportunity for therapeutic intervention.

Colony-stimulating factor-1 (CSF-1), a hormone that circulates in the bloodstream, is the primary regulator of survival, proliferation and differentiation of tissue macrophages, including TAMs. CSF-1 controls macrophage functions by binding to and activating its specific cell surface CSF-1 receptor (CSF-1 R). In a mouse model of mice with mammary gland tumors that metastasize to the lung, CSF-1 produced by tumor cells enhanced tumor progression and metastasis by recruiting TAMs to the tumor sites. The TAMs produced factors that stimulated the blood vessel formation needed for tumor progression, and produced tumor cell growth factors and destructive enzymes that increased tumor cell invasion and metastasis. For this reason, CSF-1 and CSF-1 R are currently targets for new anti-metastatic therapies. Thus, understanding CSF1/CSF-1 R signaling pathways should provide new therapeutic targets in breast cancer. Furthermore, a newly discovered myeloid growth factor, interleukin 34 (IL-34), recently shown also to act through CSF-1 R, could also enhance mammary tumor progression and metastasis. A novel CSF-1 R-mutation-based approach was used to lessen the complexity of CSF-1 R signaling in analyzing the macrophage signals important for tumor progression and metastasis. A "minimal CSF-1 R," which is involved in signaling pathways for tumor progression and metastasis, was identified. In addition, the function of IL-34 in comparison with CSF-1 is being actively explored. Understanding the regulation of CSF-1 R signaling pathways in tumor progression and metastasis will provide another opportunity to target breast cancer.

Shuaili Chen, Ph.D., Cold Spring Harbor Laboratory, "Gene Copy Number Analysis and Identification of Molecular Biomarkers From Locally Advanced Breast Cancers," Robert Lucito, Ph.D., mentor. $120,000, contract number C021329, January 1, 2006 – June 30, 2008.

Over the past 20 years, the mortality rate of breast cancer has dropped steadily due to early detection and better multimodal therapy; five-year survival rates for these patients are higher than 75 percent in most developed countries [World Health Organization (WHO) 2003 data]. However, prognosis remains poor for patients with locally advanced breast cancer (LABC), which is marked by primary tumors greater than 5 cm, or with ipsilateral internal mammary lymph node involvement, or direct involvement of the skin/chest wall, representing clinical

stages IIB through IIIB (Hortobagyi 1990; Wolff and Davidson 2002). The five-year survival rate could be as low as about 30 percent (McIntosh, Ogston, Payne, Miller, Sarkar, Hutcheon and Heys 2003).

In this study, computer analyses were performed, first, to identify the genes that are frequently altered and second, to compare these genes to those already identified as frequently altered in common forms of breast cancer, to determine whether LABC could be distinguished.

Clinical collaborators at New York University Medical Center obtained 27 samples, of which only ten were of a quality that could be molecularly analyzed. Nevertheless, analysis was continued, and regions of amplification and deletion were identified as planned. It was determined that there were few genomic aberrations in the LABC samples as compared to more common forms of breast cancer.

Alterations in LABC might be due to epigenetic silencing. Fortunately, a sensitive method to identify one type of epigenetic alteration, DNA methylation, had previously been developed at the Cold Spring Harbor Laboratory. This method was used to analyze the LABC samples, and it was determined that the numerous methylation events could classify these samples as a rarely seen type of cancer termed methylator phenotype. LABC samples had never been analyzed for methylation, and thus, this phenomenon was not previously observed. Together with the increased level of methylation, this factor may be used as a clinical indicator.

Additional genomic data that may help identify the meaningful gene methylation events have been obtained. These genes will also serve as biomarkers that can be used in the clinical setting to stratify patients with different forms of breast cancer. Those genes identified will be validated, and functional studies initiated to understand what makes this type of cancer so aggressive. Furthermore, these genes likely will be the future targets of pharmaceutical drug development.

Shuang Fu, M.D., Ph.D., Columbia University College of Physicians and Surgeons, "Checkpoint Functions of the BRCA1/BARD1 Tumor Suppressor," Richard Baer, Ph.D., mentor. $120,000, contract number C021330, January 1, 2006 – December 31, 2008.

BRCA1 has been implicated in the activation of several cell cycle checkpoints induced by DNA damage, and it is thought that these checkpoints contribute to the tumor suppression activity of BRCA1. However, the molecular mechanisms by which BRCA1 mediates checkpoint control are not understood.

In vivo, BRCA1 associates with the BARD1 protein to form a potent E3 ligase that can readily catalyze ubiquitin polymerization. Polyubiquitination by the BRCA1/BARD1 heterodimer is unique because it generates an unconventional isopeptide linkage involving lysine residue K6 of ubiquitin. The resultant K6-linked polyubiquitin chains are distinct from the more common K48-linked chains that target proteins for proteasomal degradation. Thus, to understand the role of BRCA1 in the DNA damage response, it is necessary to identify the enzymatic substrates of BRCA1/BARD1 and to determine the biological consequences of their conjugation to K6-linked polyubiquitin.

Previous observations suggest that ubiquitination by BRCA1/BARD1 provides a signal that promotes chromatin binding of CtIP at sites of DNA damage and that this signal is required for proper execution of the G2/M checkpoint. Indeed, it seems reasonable to propose that K6-linked CtIP polyubiquitination by BRCA1/BARD1 is a critical signal for checkpoint activation. To explore this hypothesis, this project proposes to: 1) confirm that the polyubiquitinated CtIP

conjugates generated by BRCA1/BARD1 are indeed comprised of K6-linked chains; 2) identify proteins that specifically bind K6-linked polyubiquitin; and 3) determine the role of these proteins in CtIP chromatin association, CtIP focus formation, and G2/M checkpoint activation during the DNA damage response.

Although results previously published by this laboratory established that CtIP is ubiquitinated *in vivo* in a BRCA1-dependent fashion, the co-immunoprecipitation assay employed is not sufficiently sensitive to evaluate whether the polyubiquitin conjugates of CtIP are comprised of K6-linked chains. To ascertain this, a sensitive assay to detect BRCA1/BARD1-mediated ubiquitination *in vivo* is being developed and tested.

BRCA1 autoubiquitination, which involves formation of K6-linked chains, will be exploited to identify proteins that specifically recognize K6-linked polyubiquitin. Therefore, a yeast two-hybrid screen will be designed in which the fused sequences of both BRCA1 and BARD1 are used together as bait. For this purpose, two versions of this BRCA1-BARD1 bait, an enzymatically active form containing wildtype BRCA1 and an enzymatically inactive form containing the I26A mutation, have been constructed. The two baits are now being tested to confirm that the wildtype form, but not the I26A mutant, is autoubiquitinated with K6-linked chains upon expression in yeast. The wildtype form will then be used to screen mammalian cDNA libraries in the conventional yeast two-hybrid system. Once the false positive clones that commonly arise during two-hybrid screening are eliminated, it is anticipated that the true positive clones will fall into two classes: those that interact with the primary sequences of either BRCA1 or BARD1; and those that interact with the K6-linked polyubiquitin chains of the autoubiquitinated BRCA1-BARD1 bait. To identify the latter class, each positive clone will be tested for its ability to interact with both the wildtype and the enzymatically inactive forms of the bait. Proteins that recognize K6-linked polyubiquitin should interact with the enzymatically active, but not the enzymatically inactive, bait. Secondary analyses will then be performed to ascertain whether any of the candidate proteins also bind K6-linked polyubiquitin *in vitro* and in mammalian cells.

Corinne Leloup, Ph.D., Columbia University College of Physicians and Surgeons, "Interactions of RAD9, RAD9B, and BRCA1 in Breast Cancer," Howard Lieberman, Ph.D., mentor. $120,000, contract number C021331, January 1, 2006 – December 31, 2008.

BRCA1 loss of function is related to breast and ovarian cancers. The goal of this project is to understand better how BRCA1 is regulated; specifically, whether the RAD9 family of proteins can contribute to BRCA1 malfunction will be examined.

The influence that lack of RAD9 and/or RAD9B may have on the expression, phosphorylation or localization of BRCA1 in mouse embryonic stem (ES) cells was examined. Also addressed was whether irradiation changes the expression level and/or the phosphorylation level of BRCA1 in the same set of cells with different RAD9 and RAD9B status.

Proteins from mouse ES cells that either contain the wildtype or deletion alleles of *RAD9* and *RAD9B* genes were extracted, and the level of BRCA1 protein was examined by Western blotting.

The study findings suggest that the RAD9 family of proteins is involved in regulating BRCA1 function in mice, but results show that mouse BRCA1 is phosphorylated after gamma irradiation as human BRCA1 is. Therefore, mouse BRCA1 can be used to model human BRCA1 under some circumstances, and mouse ES cells, to study some aspects of human breast cancer.

Haiyan Lu, Ph.D./Janice Murtagh, Ph.D., Montefiore Medical Center, "Taxotere-Induced hsp90 Degradation: A Novel Mechanism of Action," Edward L. Schwartz, Ph.D., mentor. $120,000, contract number C021332, January 1, 2006 – December 31, 2007.

Taxotere is a widely used cancer chemotherapeutic drug with well-documented clinical antitumor activity against a range of human cancers, including breast, lung, prostate and ovarian cancers. Taxotere binds to microtubules, a key cytoskeletal protein in cells, and interferes with a number of cellular functions involving microtubules, including cell division. In previous studies, taxotere also decreased the expression and function of hsp90, a regulatory and chaperone protein in cells. The objective of this project is to determine whether taxotere and a related drug, laulimalide, affect hsp90 function in breast cancer cells; in particular, whether they obstruct the ability of hsp90 to mediate cell signaling and cell migration.

Breast cancer cells can be stimulated to undergo migration (a property that contributes to their invasive and metastatic properties) when treated with the growth factor EGF (epidermal growth factor). Taxotere and laulimalide inhibited the migration in response to EGF in three different human breast cancer cell lines. The inhibition was similar to that of a drug that specifically targets hsp90, geldanamycin, and these data are consistent with the hypothesis that hsp90 could be involved in the actions of taxotere and laulimalide. Experiments failed to show an effect of taxotere on the levels of hsp90 protein in the cells, as previously seen in human umbilical vein endothelial cells. Whether the expression of a number of cellular proteins for which hsp90 serves as a molecular chaperone was affected by taxol, taxotere or laulimalide was then examined. The only consistent change observed with all three drugs was a decrease in c-raf expression. In most cases, the actions of taxotere and laulimalide were comparable to those of the known hsp90-targeting drug, geldanamycin. While these experiments show that taxotere induces changes in expression of some hsp90 client proteins that are consistent with those produced by geldanamycin, it cannot be concluded that this action is due to a direct effect on hsp90, as not all hsp90 client proteins were affected.

If taxotere targets hsp90, it would interfere with the actions of geldanamycin. Therefore, an assessment of the role of hsp90 on the cellular actions of taxotere was made by determining whether it affects the proliferation and other molecular actions of geldanamycin. While both drugs inhibit breast cancer cell proliferation, their effect together was at best additive, and in many cases appeared to be less than additive. This finding suggests that the two agents may target similar or overlapping pathways to produce their cytotoxic effects.

A more complete understanding of the mechanisms of action of taxotere could lead to refinements in its use in the treatment of breast cancer, and could provide new avenues to explore for discovery of anti-cancer drugs.

Luca Grumolato, Ph.D./Sapna Vijayakumar, Ph.D., Mount Sinai School of Medicine, "Role of the New Wnt Receptor Ryk in Breast Tumor Progression," Stuart Aaronson, M.D., mentor. $120,000, contract number C021333, January 1, 2006 – December 31, 2008.

The great majority of deaths from breast cancer arise from the cancer's spreading from the breast to another site such as bone. Breast cancer cells in bone can cause bone-forming or bone-destroying damage. A pathway for normal bone development can be altered by breast cancer cells. This study aims to determine how interaction between breast cancer cells and the normal bone development pathway could lead to bone cancer.

Experiments conducted to date did not show ane interaction of Wnt 3a ligands with the receptor Ryk. Since the hypothesis of the original proposal was based on the understanding that canonical Wnt ligands interact with Ryk, lack of such interaction between the two molecules undermines the biological significance of the proposal. Based on recent findings about the importance of Wnt signaling in bone metastasis induced by different cancer types, the study now investigates the effect of paracrine Wnt signaling on breast cancer-induced bone metastasis.

This laboratory has identified in breast cancer cells high levels of a protein, DKKI, that antagonizes the bone development pathway. Breast cancer cells with DKKI levels diminished by approximately 90 percent have been injected into the bones of mice to determine whether breast cancer cell-mediated bone cancer would be enhanced by decreasing DKKI activity. The study is not yet complete.

Experimental conditions have also been developed to apply a variety of breast cancer cells to this study with their secretions diminished. These studies will provide insight into what factors in breast cancer cells lead to metastic bone cancers in the mice.

Jianli Gong, Ph.D., Lu-Hai Wang, Ph.D., Mount Sinai School of Medicine, "Apoptosis of Breast Cancer Cells: Role of RACK1/CIS and STAT3/GSK3β/Twist Signaling," Toru Ouchi, Ph.D., mentor. $120,000, contract number C021334, January 1, 2006 – December 31, 2008.

RACK1 is a seven WD-motif containing protein with multiple downstream effectors and is known to regulate various cellular functions. Dynein light chain was discovered to be a novel partner of RACK1, and RACK1 was shown to be associated with BimEL and DLC1 upon apoptotic stimulation. This study further explores the role and mechanism of RACK1-DLC1-mediated regulation of BimEL, especially in BimEL degradation through ElonginB/C-Cullin2-CIS E3 ligase complex, and assess its significance in drug-induced cancer cell apoptosis to develop potential therapeutic agents for breast cancer.

Twist is a highly conserved basic helix-loop-helix (bHLH) transcription factor. In addition to its role in development, Twist has gained attention for its major role in cancer progression. Studies have shown that Twist is able to promote cancer hallmarks, such as evasion of apoptosis, and sustaining angiogenesis and metastasis. This study further assesses the biological and clinical significance of the regulation of Twist by GSk3β and STAT3, and elucidates the mechanism of GSK3beta and STAT3-mediated regulation of Twist.

The research has shown that RACK1 formed a triple-complex with DLC1 and BimEL, in the presence of apoptotic agents; BimEL formed a complex with DLC1 and BimEL in the same fractionation, using velocity sedimentation in glycerol gradient; RACK1 inhibited the release of BimEL from microtubule upon paclitaxel treatment; centrosomal translocation of BimEL by DLC1 was required for RACK1-mediated degradation of BimEL; STAT3 transcriptionally activates Twist in regulating invasion and anchorage-independent survival of breast cancer cells; GSK3β was able to promote Twist phosphorylation *in vitro* and in cells, which is LiCl-sensitive; and co-expression of wildtype GSK3β or activated (ca) GSK3β and Twist resulted in its exiting from the nucleus, as shown by immuno-staining and subcellular fractionation.

Future directions include the following: 1) GSK3 β-mediated regulation of Twist will be elucidated by investigating the effect of physiological activation and inactivation of GSK3 β on Twist phosphorylation, and localization and mapping the GSK3beta phosphorylation sites on

Twist; and 2) the role of STAT3- and GSK3β -mediated regulation of Twist in oncogenic properties of breast cancer cells will be assessed.

Fei Chen, M.D., Ph.D., New York University School of Medicine, "Distinct Regulation of Breast Cancer Growth by Two Isoforms of Androgen Receptor Coactivator, ARA70α and ARA/0ß." Peng Lee, M.D., Ph.D., mentor. $120,000, contract number C021335, January 1, 2006 – December 31, 2007.

To elucidate the functional relevance of ARA70α and ARA70β in breast cancer, the goals of this study were to: test the hypothesis that ARA70α/ELE1α induces growth arrest, and ARA70β/ELE1β promotes cell growth and invasion in the MCF7 and MDA breast cancer cell line and nude mice xenografts; and determine the association between breast cancer metastasis, and Herceptin resistance and altered ARA70α/ELE1α and ARA70β/ELE1β expression.

Key research accomplishments include: establishing stable cell lines that overexpress full-length ARA70α/ELE1α in MCF7 and MDA321 breast cancer cells; establishing stable cell lines that overexpress internally spliced ARA70β/ELE1β in MCF7 and MDA321 breast cancer cells; establishing stable cell lines with ARA70α/ELE1α knockdown by RNA interference (shRNA) technology in MCF7 breast cancer cells; determining that ARA70β promotes MCF7 breast cancer cell growth both *in vitro* and *in vivo*; determining that ARA70β promotes MCF7 breast cancer cell invasion *in vitro*; and determining that selected metastatic (n=75) and control cases (n=75) matched with grade and stage.

Production of monoclonal ARA70α and ARA70β isoform-specific antibodies is in process.

Study results show that ARA70β overexpression promoted cell growth of MCF7 cells, increased its degree of malignancy by colony formation in anchorage-independent assays and stimulated tumor growth in nude mice xenografts; and that ARA70β increased the invasion ability of MCF7 cells. While some of these experiments carry *in vitro* data and need confirmation from *in vivo* experimental results, these findings nevertheless support the hypothesis.

Jayakumar R. Nair, Ph.D./Mariola Kulawiec, Ph.D., Roswell Park Cancer Institute, "Mitochondrial DNA Instability in Breast Tumorigenesis," Keshav K. Singh, Ph.D., mentor. $120,000, contract number C021336, April 1, 2006 – March 31, 2008.

In order to understand the role of mtDNA mutations in breast tumorigenesis, cybrid cell lines of identical nuclear background but differing in mtDNA genotype were created. Two breast cancer cell lines carrying mtDNA mutations were used as mitochondria donors: MDAMB435 and MDAMB231. The response of these cells to treatment with the apoptosis-inducing drugs, TRAIL and etoposide, was compared with that of wildtype cybrids containing mitochondria from platelets of a healthy volunteer and lacking mutations in mtDNA. Cell viability after treatment with these drugs was measured using the MTT assay, the colorimetric assay that measures the reduction of a tetrazolium component (MTT) into an insoluble formazan product by the mitochondria of viable cells. All three tested cell lines were determined to be resistant to TRAIL. Treatment with an inhibitor of the enzyme topoisomerase II – etoposide resulted in differential response of MDAMB231 cybrid cell lines compared to 143B wildtype cybrids and MDAMB435 cybrids. MDAMB231 cybrid cells were determined to be resistant to etoposide treatment. Therefore, the nature of mtDNA mutations influences cell death after etoposide treatment. This

study suggests that mtDNA mutations present in these cybrids may contribute to breast tumorigenesis by resistance to apoptotic cell death.

Jun Yang, M.D., Ph.D., Roswell Park Cancer Institute, "PCBs Exposure, CYP1A1 Polymorphism and Breast Cancer Risk," Kirsten B. Moysich, Ph.D., mentor. $120,000, contract number C021337, January 1, 2006 – December 31, 2008.

The study will attempt to determine the role of the environmental contaminants, PCBs, in breast cancer by comparing populations of healthy control women to those with breast cancer. Post-menopausal and premenopausal women with breast cancer are being evaluated for their body burden of PCBs and their genetically variant forms of an enzyme, CYPIAI, which could metabolize PCBs to cancer-causing forms. A number of other factors that could modify the effects of PCB concentrations and CYPIAI variants will be investigated, including: serum lipid levels, age, years of education, race, smoking status, years of smoking, number of cigarettes per day, age at menarche, age at first child's birth, number of live births, lactation status, total months of lactation, age at menopause, height and weight, menopausal status, hormone replacement therapy use and years of use, and family history of breast cancer. Also, the body burden of those PCBs that increase the levels of a specific variant of CYPIAI in breast tissue will be examined in healthy controls and postmenopausal breast cancer cases.

Paul Gao, M.D., Ph.D., Memorial Sloan-Kettering Cancer Center, "Characterization of a Novel Jak/Stat Inhibitor for the Treatment of Breast Cancer," Jacqueline Bromberg, M.D., Ph.D., mentor. $120,000, contract number C021338, January 1, 2006 – December 31, 2007.

Signal transducer and activator of transcription 3 (Stat3) are constitutively activated in approximately 50 percent of primary breast cancers. A number of different mechanisms responsible for Stat3 activation, including abnormal activation of upstream signals such as Janus kinases (Jaks), has been implicated in breast cancers. Six breast cancer-derived cell lines expressing high or low levels of activated Stat3, as well as primary breast cancer specimens, were examined. Results showed that a pan-Jak inhibitor P6 treatment resulted in complete abrogation of activated Stat3 and inhibition of cell growth in the cell lines. Jaks are required for cytokine signaling, and the glycoprotein 130 (gp130) receptor-associated Jaks are known mediators of Stat3 activation. Blockade of the gp130 receptor or sequestration of gp130 ligand interleukin-6 (IL-6) led to a decrease of activated Stat3 levels. Conditioned media from those cell lines expressing high levels of activated Stat3 contained IL-6 and were capable of causing Stat3 activation. In addition, IL-6 levels in primary breast tumors were examined, and a positive correlation between activated Stat3 and IL-6 levels was found. Furthermore, the research showed that a natural Stat3 inhibitor, resveratrol, and a newly developed oral available pan-Jak inhibitor, INCB16562, also inhibited breast cancer-derived cell line growth, both *in vitro* and *in vivo*. In summary, the research led to the discovery that a principal mechanism of Stat3 activation in breast cancer occurs through the IL-6/gp130/Jak/Stat3 pathway.

This novel finding will unquestionably lead the way to developing a new therapeutic strategy targeting this pathway to treat malignancies such as breast and lung cancers more efficiently.

Cristina L. Agbunag, Ph.D./Yutaka Takigawa, Ph.D., Weill Medical College of Cornell University, "Characterization of Wnt5a," Anthony M.C. Brown, Ph.D., mentor. $120,000, contract number C021339, January 1, 2006 – December 31, 2008.

Wnt5a transgenic mice were generated and crossed to the MTB strain that expresses rtTA under the control of the MMTV-LTR promoter. Conditional expression of the transgene is driven by the presence of doxycycline (Dox), a derivative of tetracycline. Mendelian transmission of the transgene and reverse transcriptase-polymerase chain reaction (RT-PCR) analysis showed that Wnt5a transgene RNA was detected in the mammary glands of Wnt5a/MTB transgenic mice treated with Dox, and not in untreated bitransgenics or in either of the parental strains alone. The magnitude of induction was more than 200 fold. The influence of the Wnt5a transgene on early development of mouse mammary glands was studied. Transgene expression was induced for a four-week period, starting at six weeks of age, but no significant effects on mammary development were observed. Other experiments were performed to generate additional bitransgenic Wnt5a/MTB mice and induce them with Dox at a younger age (four weeks) and for a longer duration (eight weeks). Although there was considerable variation in the degree of mammary development among individual animals, these experiments did not allow the conclusion that these changes were consistently the result of transgene induction. It should be noted that animal experiments were suspended for three months during this period since it was necessary to transfer the mice to a different animal facility, requiring their quarantine and interruption in breeding.

Since no definitive phenotypic effects of the Wnt5a transgene are yet evident, one possibility is that Wnt5a acts as a tumor suppressor, as suggested by the loss of Wnt5a in several human breast cancers, rather than providing a proliferative signal. A test of this hypothesis would be to ascertain whether endogenous Wnt5a expression is reduced or lost in mouse mammary tumors, and to determine whether maintenance of Wnt5a expression from the transgene prevents tumorigenesis.

Such experiments would be potentially valuable, but would require a large commitment of time and resources to achieve statistical significance. Before embarking on such a course, the level of transgene expression in the Wnt5a transgenic lines was more quantitatively evaluated. Although the transgene is strongly inducible, its expression level relative to endogenous Wnt5a expression should be determined. Therefore, RT-PCR using primers specific for the Wnt5a transgene, together with primers that react with total Wnt5a RNA (endogenous + transgene), was performed. The Ct values again showed robust induction of the transgene in Dox-treated bitransgenics, but the total amount of Wnt5a mRNA between these mice and the controls was only slightly different. This finding implies that the level of transgene expression is similar to that of endogenous Wnt5a, or possibly lower. To address this question more definitively, Wnt5a protein levels in mammary cells from these animals will be analyzed using primary cell culture and induction with Dox *in vitro*. This work should yield greater sensitivity, since the cultures will be predominantly epithelial cells, and will require far fewer animals, since cultures from the same animal can be examined with and without Dox treatment *in vitro*.

Shengyu Yang, Ph.D., Weill Medical College of Cornell University, "Migrastatin Analogues That Inhibit Breast Cancer Metastasis," Xin-Yun Huang, Ph.D., mentor. $120,000, contract number C021340, January 1, 2006 – December 31, 2007.

Metastasis is the most common cause of cancer-related death. Development of therapeutic agents that inhibit tumor metastasis is highly desirable. In previous studies, this laboratory has identified Migrastatin analogues that inhibit breast cancer metastasis. The current project is

designed to identify and verify the protein targets of Migrastatin analogues. Moreover, the potential of store-operated calcium channel blockers as breast cancer metastasis inhibitors is being explored. The protein target of Migrastatin analogues has been identified. An actin-bundling protein from 4T1 mouse breast tumor cells has been purified with the affinity column. The crystal structure of this target has been obtained, and the critical residues involved in the binding of migrastatin analogues have been singled out.

This project also aims to search for metastasis inhibitors to calcium channel blockers. Data indicate that calcium influx is required for the migration and invasion of human breast cancer cells. Inhibitor screening indicates that store-operated channels are the responsible channels. The essential roles of store-operated channels were further confirmed by RNA interference of the recently identified store-operated channel regulators Stim1 and Orai1. Furthermore, this research showed that Orai1 mRNA levels are increased in tumor samples from breast cancer patients.

APPENDIX VIII

2007 SYMPOSIUM PRESENTATIONS AND POSTERS

PRESENTATIONS

Novel Vector to Promote Radiosensitivity and Apoptosis in Breast Carcinoma

Contract # C020906
Zhi-Jian Liu, Irina V. Lebedeva, Zhao-Zhong Su, Devanand Sarkar and Paul B. Fisher
Departments of Urology, Neurosurgery and Pathology
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Barriers to effective gene therapy, particularly for the treatment of cancer, include potency and specificity. This research aims at improving the efficacy of gene therapy through two strategies, namely, combination gene therapy with irradiation, and constructing a new and enhanced therapeutic virus that simultaneously expresses two cancer-specific therapeutic genes (a bipartite virus). To achieve these objectives, adenoviruses (Ads) were engineered to express the novel cancer-specific, apoptosis-inducing cytokine; melanoma differentiation-associated gene-7/interleukin-24 (Ad.*mda*-7); tumor necrosis factor-related apoptosis-inducing ligand (TRAIL;Ad.*TRAIL*); and a bipartite Ad simultaneously expressing both *mda*-7/IL-24 and TRAIL (Ad.*mda-7.TRAIL*) under the control of the cytomegalovirus (CMV) promoter. These engineered Ads were expanded and titered, and their biological functions evaluated in a series of human breast cancer cell lines. Infection with a similar titer of these Ads resulted in comparable levels of expressed proteins, i.e., MDA-7/IL-24, TRAIL or both gene products.

In general, the bipartite adenovirus (Ad.*mda*-7.*TRAIL*) demonstrated enhanced effects in inhibiting cell growth and inducing apoptosis in breast cancer cell lines, in comparison with viruses expressing *mda*-7/IL-24 or TRAIL alone. A significant effect was observed when specific breast cancer cell lines were infected with as few as 10 pfu (plaque forming units)/cell of the bipartite virus. In contrast, significant biological effects were usually observed when breast cancer cells were infected with 50 or 100 pfu/cell of a therapeutic Ad-expressing *mda*-7/IL-24 or TRAIL alone. The cooperative effects of *mda*-7/IL-24 and TRAIL could be relevant and suggest potential applications for breast cancer therapy. The sensitivity of different breast tumor cell lines to *mda*-7/IL-24, TRAIL and the bipartite Ad varied. The differential growth-inhibitory and apoptosis-inducing effects of these therapeutic Ads may relate to differences in cell membrane receptors permitting viral entry and/or mediating response to these molecules. The expression level of Coxsackie-adenovirus receptor (CAR) is an established molecule that defines infectivity of therapeutic Ads in mammalian cells. Moreover, both MDA-7/IL-24 and TRAIL generate specific biological functions through interaction with their respective membrane receptors: IL-20R1, IL-20R2 and IL-22R1 for MDA-7/IL24; TRAIL-R1 (or death receptor 4, DR4) and TRAIL-R2 (or death receptor 5, DR5) for TRAIL. Differences in these receptors may also explain the lack of a enhanced combinatorial effect of *mda*-7/IL-24 plus TRAIL (in the bipartite Ad) in specific breast cancer cell lines.

The primary aim is to investigate the effect of combinational treatment with irradiation and the newly developed therapeutic Ads. Studies to date show that the combination of therapeutic Ads and γ-irradiation produces enhanced inhibition in cell growth and colony formation, and promotes apoptosis in breast cancer cells. The second aim is to determine the effect of the

bipartite and single Ads, and the combinational treatment of therapeutic Ads and irradiation in a mouse breast cancer xenograft model. This is a mandatory step ultimately to translate the results of *in vitro* and potential *in vivo* effects into the clinic. The third aim is to investigate the mechanism underlying the synergistic effect of a bipartite Ad expressing both *mda*-7/IL24 and TRAIL. It is hypothesized that the combination of low concentrations of TRAIL and MDA-7/IL-24 proteins promotes changes in defined signaling pathways leading to cell death through cross-talk between the induced pathways, while lower levels of a single protein would prove inactive.

The Role of PTEN in Mediating Indomethacin Anti-Cancer Activity

Contract # C020910

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Tumor suppressor PTEN is one of the most mutated genes in human cancers. PTEN is known as a lipid phosphatase for inactivating the PI3K/Akt cell survival pathway. Evidence was gathered to link PTEN and the mitogen-activated protein (MAP) kinase-signaling pathway, an important oncogenic pathway known to promote cancer cell survival and growth. Extracellular signal-regulated kinases 1/2 (ERK1/2) are the prototype MAP kinases that can be inactivated through dephosphorylation by a family of dual threonine/tyrosine phosphatases, such as MKP2 (mitogen-activated protein kinase phosphatase 2). Data obtained here demonstrate that PTEN induces MKP2 and suppresses ERK1/2 activity, which mediates cancer cell death in response to oxidative stress and chemotherapeutic agents such as indomethacin. It was found that cancer cells with high levels of PTEN were easier to kill by indomethacin, whereas lack of PTEN confers indomethacin resistance. Indomethacin reduces the activation of ERK1/2, whereas ectopic induction of both PTEN and MKP2 in breast cancer cells leads to greater suppression of the ERK-signaling pathway.

Mechanistic study reveals that PTEN induces MKP2 by acting on chromatin and physically interacting with the MKP2 promoter. Interestingly, breast cancer cells became super-sensitive to indomethacin when MKP2 was overexpressed, suggesting that MKP2 acts as a potent cell death mediator in response to indomethacin treatment. These results are consistent with recent findings here on MKP2-mediated apoptosis that can also be regulated by other important tumor suppressors, including p53 and E2F-1. Collectively, these data suggest that PTEN plays a critical role in mediating indomethacin anti-cancer activity by upregulation of MKP2 and subsequent inhibition of MAP kinase signaling, and that MKP2 acts as a convergent target of potent tumor suppressors in mediation of cancer cell death. These new findings provide valuable information for clinical application of PTEN and its anti-oncogenic function to improve indomethacin-related treatment and develop new breast cancer therapeutic strategies.

Association Between Incident Breast Cancer and Geographic Location of Residence in the Women's Health Initiative Observational Study

Contract #C020920

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Past epidemiologic studies suggest an association between breast cancer and geographic location of residence, with a greater incidence and mortality of breast cancer at northern

latitudes. This association may be explained, in part, by exposure to vitamin D, which has been hypothesized to protect against cancer development due to its anti-proliferative, pro-differentiating and apoptotic-promoting properties. Sunlight exposure is the primary source of vitamin D. Humans are able to synthesize vitamin D from a cholesterol precursor in their skin upon exposure to ultraviolet B radiation. Therefore, individuals residing in different regions of the U.S. may experience more or less sunlight exposure, and thus varying vitamin D synthesis. Among women (50-79 years) who participated in the Women's Health Initiative Observational Study (n=93,676) and who were free of cancer (not including non-melanoma skin cancer) at baseline enrollment (1994-1998), it was proposed to investigate associations between incident breast cancer (over some seven years of followup) and the following proxy measures for vitamin D exposure: 1) region of residence at birth; 2) region of residence at baseline enrollment; and 3) clinic center solar irradiance.

***Analyses*:** Crude and adjusted hazards ratios (HRs) and 95-percent confidence intervals (95-percent CIs) for incident breast cancer were estimated using Cox proportional hazards models among women in quintiles for solar irradiance measured in Langleys and Watts (with quintiles two through five compared to one), and among women in the northern, middle, and outside the U.S. region of residence at birth, or baseline, compared to women in southern regions of residence at birth, or baseline. HRs were adjusted for age, ethnicity, education, weight, family history of breast cancer, age at menarche, age at menopause, parity, age at first birth, hormone therapy duration of use, and alcohol intake. Additional adjustment of this multivariate model for vitamin D from diet and supplements was also investigated to ascertain whether intake of vitamin D explained the observed associations. Linear trends were also studied to examine associations between incident breast cancer and the exposure variables. Additional analyses were conducted to determine whether the observed associations differed by tumor characteristics: breast cancer type (invasive versus *in situ*); estrogen receptor status (ER+/ER-); progesterone receptor status (PR+/PR-); combined ER and PR status (ER+/PR+, ER-/PR+, ER+/PR-, ER-/PR-); tumor size (<0.5 cm, > 1-2 cm, >2-5 cm, >5 cm), lymph node involvement (yes, no); and tumor grade (well differentiated, moderately differentiated, poorly differentiated, anaplastic). Tests for competing risks were used (p value < 0.05 considered statistically significant). Also investigated was the potential for effect modification by the following factors: age; ethnicity; the Gail five-year risk score (< 1.25, 1.25-1.74, ≥ 1.75); total vitamin D intake; total calcium intake; and total vitamin D and calcium intake (low vitamin D/low calcium, high vitamin D/low calcium, low vitamin D/high calcium, high vitamin D/high calcium); participant's skin reaction to the sun as reported at year four (no change, tans/no burns, burns/then tans, burns/then minimal tan, burns/no tan); time spent outside in daylight hours in the summer as reported at year four follow-up (< 30 minutes, 30 minutes to 2 hours, > 2 hours); and time spent outside in daylight hours in other seasons as reported at year four (< 30 minutes, 30 minutes to 2 hours, > 2 hours). Interactions were tested using the Likelihood Ratio Test (p value < 0.05 considered statistically significant). Exploratory analyses were also conducted to evaluate the relationship between breast cancer incidence and time spent in the sun as reported at year four, as well as the relationship between breast cancer incidence and a combination variable incorporating time spent outside and location of residence.

Vitamin A Metabolism and Breast Cancer

Contract # C020921
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Breast cancer is the most common malignancy in women in the United States, causing more than 40,000 deaths each year. Retinoids, which include vitamin A (retinol) and its natural and synthetic derivatives, are very important for many biological processes and well known as promising drugs to prevent and treat various cancers. The use of ATRA (all-trans retinoic acid) to treat acute promyelocytic leukemia (APL) is one such successful example, suggesting that retinoids can be used as drugs to treat human breast cancer.

Aberrant vitamin A metabolism may promote the development of various cancers. The normal human breast takes up vitamin A and stores it as esters. An enzyme, LRAT, catalyzes the formation of the esters. The level of LRAT is high in normal human breast, but very low in breast cancer cells. The hypothesis is that human breast cancer cells lack LRAT, which leads to a local retinoid deficiency in the tumor. It is expected that restoring LRAT would increase retinol storage and might suppress tumor progression. The goals of this project are to define the molecular mechanisms resulting in low levels of LRAT in breast cancer, and to devise new therapeutic approaches to restore LRAT and inhibit tumor growth.

Preliminary results indicated that LRAT is present at a higher level in normal human breast than in breast cancer cells. Experiments showed that differences in various transcription factors might cause the loss of LRAT in breast cancer cells. This project should lead to identification and study of these transcription factors, yielding new therapeutic approaches to treat human breast cancer.

Results from this project should improve understanding of vitamin A metabolism in breast cancer, and help identify new therapeutic approaches to treat human breast cancer.

Rack1 and CIS Mediate the Degradation of BimEL in Cancer Cells

Contract # C021334
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Receptor for activated C kinase 1 (RACK1) is a seven WD-motif containing protein with numerous downstream effectors regulating various cellular functions. Using yeast two-hybrid screen, dynein light chain 1 (DLC1) was identified as a novel interacting partner of RACK1. Additionally, RACK1 formed a complex with DLC1 and Bcl-2-interacting mediator of cell death (Bim), specifically BimEL, in breast cancer cells treated with apoptotic agents, including paclitaxel and staurosporine. DLC1 was important, but not absolutely required, for the interaction between RACK1 and BimEL. Upon paclitaxel treatment, RACK1 mediated the degradation of BimEL by forming a complex with ElonginB/C-Cullin2-CIS E3 ligase. Overexpresion of RACK1 led to accelerated BimEL degradation, while knockdown of RACK1 resulted in BimEL accumulation upon paclitaxel treatment of the cells. Physical interactions were found between RACK1 and CIS/Cul2, and BimEL and CIS/Cul2. CIS-based E3 ligase

complex played an important regulatory role in RACK1-mediated BimEL ubiquitination and degradation. Downregulation of CIS led to BimEL accumulation, and overexpression of CIS and Cul2 resulted in constitutive degradation of BimEL.

It was further demonstrated that RACK1 conferred resistance of breast cancer cells to paclitaxel *in vitro* and *in vivo*. Overexpression of RACK1 in MCF7-I4, an invasive line derived from MCF7 cells, protected cells from undergoing anoikis, promoted anchorage-independent growth in the presence of paclitaxel *in vitro,* and resulted in resistance to paclitaxel in tumorigenesis in nude mice. Knock-down CIS and RACK1 in MCF7 cells increased the sensitivity of cells to anoikis and paclitaxel treatment. Finally, an inverse correlation was observed between CIS and BimEL levels in both ovarian and breast cancer cell lines and clinical specimens. This study suggests a role for RACK1 in protecting cancer cells from apoptosis by regulating the degradation of BimEL, which, together with CIS, could play an important role in drug resistance during chemotherapy. Intervention of interaction between RACK1 and BimEL or DLC1 could enhance the efficacy of killing cancer cells by paclitaxel.

POSTERS

Function of BRCA1 in the Maintenance of DNA Replication Fork Integrity

Contract # C020907
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The DNA molecule carries the genetic information necessary for cells to grow, divide and develop normally. This information is replicated faithfully before cell division. However, the DNA is constantly subjected to damaging events of external or physiological origin. Occurrence of DNA damage alters the genomic sequence that may lead to cancer development. To avoid genomic instability, cells have evolved mechanisms preventing cell division in the presence of DNA damage and promoting DNA repair. The BRCA1 protein has been implicated in various cellular processes, including homologous recombination (HR) DNA repair, transcriptional regulation, chromatin remodeling, mitotic spindle assembly and cell cycle checkpoint regulation.

BRCA1 forms a functional heterodimer with BARD1, which is required for proper localization of the complex, E3 ligase activity, DNA-binding and protein stability. In addition, BRCA1/BARD1-deficient cells are hypersensitive to DNA cross-linking agents, such as cisplatin and mitomycin C. Using Xenopus cell-free systems, the role of the BRCA1/BARD1 complex was studied at the replication fork, in DNA repair and in checkpoint activation following replication of interstrand cross-link (ICL) DNA damage. Studies addressing specifically the repair of ICLs have been hampered by the heterogeneous nature of the lesions arising from cross-linking agents. To overcome this limitation a model system was established to recapitulate DNA damage signaling and DNA repair of a single ICL that models a cisplatin cross-link, in the absence of other DNA lesions. Using this system, it was demonstrated that a plasmid harboring a single ICL replicates and forms concatemer DNA molecules, as predicted.

Notably, the ICL-containing plasmid replicates less efficiently than a control, undamaged plasmid. This inhibition can be abrogated using the ATM and ATR inhibitor caffeine, which greatly increases the accumulation of unrepaired replicated molecules. To distinguish between

these two pathways, the phosphorylation of Chk1 was monitored on S345, a target of ATR activation and ATM autophosphorylation at S1981 that correlates with ATM activation. Chk1 but not ATM phosphorylation was observed following ICL plasmid replication, strongly suggesting that the ATR, but not ATM, pathway is activated. Moreover, monitoring DNA replication of the ICL-containing plasmid over a longer time-course showed the appearance and accumulation of a labeled DNA molecule corresponding in size to a circular, repaired DNA molecule. This observation was confirmed by the generation of a polymerase chain reaction (PCR) product across the original location of the ICL. Altogether, this system will enable addressing the role of the BRCA1/BARD1 complex in the ICL signaling and repair processes.

RNAi: A Therapeutic Approach for the Treatment of Breast Cancer

Contract # C020911
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Breast cancer is a complex disease that requires a multifaceted treatment plan. Normal cells can develop into tumor cells when certain genes become activated, resulting in uncontrolled cell growth. Treatment of breast cancer can be broken down into three general categories: 1) local or regional, 2) systemic, and 3) alternative and holistic. Typically, local surgical treatments are supplemented by systemic treatments, such as chemotherapy. The success of chemotherapy relies on the ability of drugs to kill rapidly dividing cancer cells. One cause of chemotherapy failure is resistance of cancer cells to anti-cancer drugs. This phenomenon is termed multidrug resistance, or MDR. The classical MDR phenotype is due to overexpression of P-glycoprotein (P-gp). P-gp acts as an efflux pump that expunges drugs from cancer cells.

Research has been aimed at developing strategies for suppressing the effects of P-gp-induced MDR. One such approach has targeted suppression of messenger RNA (mRNA) from the MDR1 gene, thus preventing the synthesis of P-gp altogether. RNA interference (RNAi) has been gaining attention as an alternative method for silencing specific gene expression. RNAi is mediated by short-interfering RNAs (siRNAs) generated from double-stranded RNA. siRNAs can trigger silencing of gene expression by inducing degradation of the complementary mRNA. siRNA-mediated RNAi has significant potential to modulate protein-dependent disease states, such as MDR and uncontrolled growth.

As with other forms of gene therapy, therapeutic application of siRNA *in vivo* will require overcoming several biological barriers. Like DNA, siRNAs are large, negatively charged molecules. Their size and charge prevent them from entering a cell by simple diffusion across the cellular membrane. Even when siRNAs enter a cell, they are quickly degraded. Thus, siRNAs require a delivery system for transport to the cell surface, across the cellular membrane, and to the interior of the cell. Various delivery vectors for siRNA have been tested. Viral vectors are very efficient, but concerns have been raised about their immunogenicity. Focus has shifted to nonviral delivery vectors, such as positively charged lipids. However, these vectors provided only poor delivery in animal models due to their thermodynamic instability and rapid clearance by the immune system.

Water-soluble positively charged polymers (i.e., polycations) are promising nonviral delivery systems. In general, the success of nonviral vectors has been limited by poor transfection efficiency. However, a new class of polycations, designed and synthesized here, holds greater potential than previously characterized transfection reagents for *in vivo* applications. These

polycations have positively charged sidechains that promote complexation with negatively charged nucleic acids like DNA or RNA. Through this electrostatic interaction, polycation/nucleic acid complexes achieve size condensation and charge neutralization, or an overall positive complex charge.

The positively charged complexes interact favorably with the negatively charged cell surface, promoting binding and uptake of the complexes. This research project aims to examine libraries of polycations as delivery vectors for siRNA directed against various gene targets, such as MDR1 in drug resistant cells, and genes responsible for uncontrolled growth (e.g., Her2/neu/ErbB2, c-myc, or c-met) in human breast cancer cells.

Regulation of Breast Cancer-Related Nuclear Factors by NAD^+

Contract # C020912
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Cancer often results from DNA damage. A number of proteins in the cell nucleus repair DNA damage and maintain genome stability, and therefore protect cells from tumor formation. Two of these proteins, PARP-1 [a poly (ADP-ribose) polymerase] and SIRT1 (a protein deacetylase), are unique because they require a small molecule, NAD^+, for their activity. Both PARP-1 and SIRT1 degrade NAD^+, and use the degradation product for chemical modifications of nuclear proteins. These modifications significantly change the function of the acceptor proteins, affecting their interaction with DNA and other proteins. PARP-1 and SIRT1 are key regulators of cellular stress response and survival, and may play a critical role in the development of breast cancer through two means: (1) maintenance of genomic stability; and (2) direct regulation of breast cancer-related proteins, such as estrogen receptors (ERs). Studies on dietary deficiency of NAD^+ suggest a correlation between NAD^+ metabolism and development of cancer, potentially through regulation of PARP-1 and SIRT1 functions. However, little is known about how NAD^+ synthesis in the cell regulates PARP-1 and SIRT1 activities.

The central hypothesis of this project is that nuclear NAD^+ production is a key regulator of PARP-1 and SIRT1 activities, and that this action of NAD^+ controls breast cancer cell function. The specific questions addressed here are: 1) how do NMNAT-1 and NAMPT, two enzymes in the nuclear NAD^+ biosynthetic pathway (the NAD^+ producers), regulate the biochemical activity of PARP-1 and SIRT1 (the NAD^+ consumers); and 2) how do NMNAT-1 and NAMPT affect the gene regulatory activity of PARP-1 and SIRT1 in MCF-7 breast cancer cells.

Using cell-free biochemical assays, specific interactions were studied between NMNAT-1 and PARP-1, and two distinct mechanisms identified for regulation of PARP-1 activity by NMNAT-1. To understand how NAD^+ metabolism regulates breast cancer cell function, MCF-7 cell lines were established with much reduced levels of NMNAT-1 and NAMPT proteins. Using these cells, the means by which NAD^+ producers regulate global gene expression in the breast cancer cells was examined. Similar approaches were taken to study the role of SIRT1 and PARP-1 in gene regulation, and the relationship between the NAD^+ producers and the NAD^+ consumers in gene regulation. The expression analyses revealed that NMNAT-1 and NAMPT had broad and overlapping effects on gene expression in MCF-7 cells. Subsets of the NMNAT-1- and NAMPT-

regulated genes are also regulated by SIRT1 and/or PARP-1, demonstrating a critical role of NAD^+ synthesis in the function of SIRT1 and PARP-1.

Future studies will focus on the genes regulated by both the NAD^+ consumers (PARP-1 and SIRT1) and the NAD^+ producers (NMNAT-1 and NAMPT). The mechanism for PARP-1- and SIRT1-dependent transcriptional regulation will be investigated. Of special interest is how NAD^+ biosynthesis modulates the activity of PARP-1 and SIRT1 in transcriptional regulation. These experiments are essential for understanding the role of NAD^+ metabolism and NAD^+-dependent enzymes in breast cancer cell function. Furthermore, small molecule regulators of the NAD^+-dependent enzymes are being tested for their action on specific NAD^+-dependent target genes to facilitate development and application of these chemicals to cancer therapy.

Characterization of Isoprenylcysteine Carboxyl Methyltransferase (Icmt)

Contract # C020915
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Cancer arises when the mechanisms that, under normal circumstances, tightly control cell growth and survival are disrupted or deranged. Numerous genes control cell growth. Those that, when mutated, promote uncontrolled cell growth are known as oncogenes. The best-studied of all oncogenes is Ras because it is associated with human cancer more frequently than any other. The signals controlled by Ras have been implicated in a variety of cancers, including breast cancer.

The protein encoded by the Ras gene functions only when it becomes associated with cellular membranes because of a relatively unique series of modifications. Three enzymes that work sequentially catalyze these modifications. It follows that drugs that interfere with one or more of these enzymes might be effective as anti-cancer drugs. Indeed, a new class of anti-cancer drugs termed farnesyltransferase inhibitors was recently developed that inhibits the first of the three enzymes. Studies here focus on the third enzyme, known as isoprenylcysteine carboxyl methyltransferase (Icmt). Recent results show the localization and disposition of Icmt in living cells.

The goal of this project is to characterize this enzyme from the standpoint of its biochemistry and cell biology to a sufficient degree for facilitating efforts by the pharmaceutical industry to develop drugs that target the enzyme.

Translational Control in Inflammatory Breast Cancer Progression

Contract # C020917
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Inflammatory breast cancer (IBC) is a highly aggressive form of breast cancer. Although its incidence is low (one to six percent of breast cancers in the United States), it is associated with a low survival rate. Little is known about the molecular basis for the development of IBC, but it has been reported that the tumors are highly adapted to hypoxia, and are very effective in inducing vascularization. There are no reports addressing the role of and important regulatory

step in cell growth, the control of initiation of protein synthesis (or "translation"), in the onset of IBC.

The aim of this project is to elucidate the role protein synthesis regulation plays in the development of IBC. In particular, under investigation are protein synthesis initiation factors implicated in other cancers, as well as other molecules shown to be important specifically for development of IBC. The system used to investigate the regulation of translation is based on cells derived from IBC patients, combined with analysis of factors of interest in patient tissue samples. Once likely candidates are identified, genetic changes are introduced into IBC cells to impair their expression. These modified cells are then utilized to study the effect of these factors in tumor growth using animal models.

By examining IBC cells and analyzing patient tissue samples, it was determined that eIF4G, a protein synthesis initiation factor, is overexpressed in IBC. To ascertain whether eIF4G is involved in tumorigenesis, its production in IBC cells was genetically impaired, and the effect of this alteration on tumor growth in mice and chick animal models was examined. It was observed that eIF4G ablation leads to a marked reduction in tumor growth in both systems. This defect is accompanied by a decrease in production of vascular endothelial growth factor (VEGF), a protein that plays a key role in induction of vacularization required for the tumor to survive, as well as reduction in the levels of E-cadherin, a molecule shown previously to be required for development of IBC. Examination of the mechanism whereby eIF4G regulates the expression of these two proteins led to the finding that eIF4G is required for efficient synthesis of VEGF protein directly, as well as ensuring that the E-cadherin stabilizing factor, p120 catenin, is efficiently synthesized. Both processes are mediated by an unorthodox mechanism of protein synthesis initiation. Identification of key players in the development of IBC should serve as a gateway to identify targets for future treatment strategies.

Determinants of Weight Gain in Women With Early Stage Breast Cancer

Contract # C020918
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Weight gain after breast cancer is common, occurring in up to 95 percent of patients whose cancer is detected early and who receive chemotherapy during treatment. A gain of approximately 15 pounds has been associated with a 50-percent greater likelihood of cancer recurrence and a 60 percent higher likelihood of death, compared to women who maintain their normal weight. Reasons for this weight gain are poorly understood and have not been carefully studied.

One reason for the weight gain may be that chemotherapy shuts down the ovaries, thereby reducing sex hormone production. While this shutdown is expected to lower breast cancer recurrence, it is also associated with weight gain and increased body fat, which is in turn associated with higher levels of sex hormone production.

Since sex hormones influence overall body weight, it is believed that changes in sex hormone levels may affect how much weight is gained after breast cancer. This relationship may be affected by a woman's genetic makeup, her diet and level of physical activity, and her psychological and social well-being. The primary goal of this study is to examine weight changes after breast cancer in relation to changes in sex hormone levels. The study involves

200 women aged 35 to 75 years who were diagnosed with early-stage breast cancer. To date, 152 participants have been recruited for the study. These women are being followed for one year. The long-term aim is to determine whether weight gain and its causal factors are related to breast cancer recurrence and overall survival. It is thought that patients with greater declines in sex hormones would gain the most weight. The study also plans to examine other factors that may contribute to the weight gain, including fatigue, characteristics of the cancer, and treatments received.

This study will be the first comprehensive examination of hormonal changes, genetic makeup, diet, physical activity, and psychological and social well-being as factors for weight gain in women with breast cancer. The outcome of this research will shed light on why so many women experience weight gain after breast cancer, and help identify those who are most susceptible, so that they may be targeted for preventive interventions.

Chemical Synthesis of Erythropoietin

Contract # C020919
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Erythropoietin (EPO) is a glycoprotein hormone that has become a leading therapeutic for the treatment of cancer-related anemia. Despite the clear-cut clinical importance of this compound, attempts at rigorous evaluation of the role of glycosylation on the activity and stability of EPO have been complicated to date by daunting difficulties associated with isolating significant quantities of homogenous EPO. It is believed that total chemical synthesis provides a unique opportunity to meet such challenges. The goal of this project is therefore to prepare synthetic homogeneous EPO and gain access to a range of EPO analogues for structure-activity-relationship investigation. Broadly speaking, an undertaking of this magnitude could well lead to development of generally useful strategies and protocols applicable to the entire field of glycoprotein synthesis.

In earlier efforts, researchers here achieved the synthesis of the fucosylated biantennary N-linked glycan and O-linked glycophorin, two essential carbohydrate components of EPO. After addressing the synthesis of the glycans, attention was turned to the assembly of the glycopeptide. A maximally convergent route to EPO would involve preparation of the four different glycopeptide fragments, which would subsequently be joined through some form of ligation to furnish the fully glycosylated protein backbone. Development of a repertoire of ligation methods could well be critical to the success of the project. In considering a strategy for the *de novo* synthesis of EPO, note was taken of the paucity of cysteine residues on the molecules. To that end, cysteine-free peptide bond-forming protocols were developed in the broad context of a phenolic ester strategy. While this method has enabled completion of the EPO 114–166 domain and the EPO 22–37 domain, it requires initial installation of an auxiliary, which must subsequently be cleaved. In practice, the auxiliary-based approach may suffer from significant practical limitations. To circumvent the issue of auxiliary removal, another major effort was initiated to pursue a direct auxiliary-free coupling strategy for glycopeptide synthesis. This effort led to successful development of two sets of powerful methods for accomplishing cysteine-free glycopeptide ligation.

The fragment-coupling possibilities, previously restricted to cysteine-based NCL and auxiliary-based, non-cysteine ligation, have now been expanded in important ways. In particular, the

metal (AgCl)- and metal-free (TCEP)-mediated acyl donor enhancement of the recently developed C-terminal ester resulted in a major expansion of options in pursuit of the total chemical synthesis of EPO.

Currently, the newly developed methods are being applied to the synthesis of the four glycopeptide fragments, and preparations are underway for the merging of these fragments to obtain the whole sequence of EPO. The final assembly will feature two AgCl-mediated fragment condensations and one NCL. Global deprotection will furnish the desired homogeneous EPO, and subsequent biological tests will be conducted.

Fragmentation of the Golgi Apparatus in Breast Cancer Cells

Contract # C021327
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Cancer cells proliferate rapidly and in an uncontrolled fashion, and there is usually damage to the cellular DNA. This rapid growth contrasts with normal cells. Normally, in response to DNA, damaged cells undergo programmed cell death termed “apoptosis”; this process effectively eliminates potentially cancerous cells from an organ. Consequently, a major question in breast cancer research is to understand how cancer cells avoid or suppress the normal apoptotic cell death pathway, and sometimes proliferate even following treatment with anti-cancer therapies. This research focuses on a class of enzymes termed phospholipase Ds (PLDs), which generate so-called “signaling lipids,” in this case, phosphatidic acid (PA). PA has been implicated in regulating many cellular processes, including growth, proliferation and cell division. Furthermore, several studies have shown that elevated levels of PLDs are present in breast carcinomas, suggesting that increased PA production contributes to tumor growth and survival.

To address how PLD protects cancer cells, a cell-free system was used to synthesize PLD and an analysis performed on how it is cleaved during apoptotic cell death and Golgi fragmentation. One of the PLDs, PLD1, was rapidly digested, whereas another form, PLD2, was relatively resistant. Strikingly, PLD1 activity was not lost following caspase cleavage, but PLD1 response to several regulatory stimuli was altered. Using recombinant DNA technology and site-directed mutagenesis, three specific caspase sites were identified and correlated with changes in the regulatory response. PLD cleavage also occured in response to cellular stress caused by the accumulation of misfolded or aggregated proteins. Cells possess families of enzymes that either participate in protein folding or dispose of the misfolded molecules. However, when cells are overwhelmed by the presence of high levels of inappropriately folded proteins, they undergo apoptosis.

The mechanism whereby cells make this commitment to apoptosis is not well understood, and these data have implicated PLDs in mediating the transition from the stress response to apoptosis. The most important finding from these studies is that, despite their proteolytic cleavage in response to apoptosis-inducing drugs, both forms of PLD retained their enzymatic activity. These data thus explain how high levels of these enzymes in tumor cells are able to promote growth and survival even in response to drugs which would be expected to kill such cells.
A cell-free system was used to synthesize PLD, and an analysis performed on how it is cleaved during apoptotic cell death and whether this correlates with Golgi breakdown.

CSF-1 Signaling in Mammary Tumor Progression and Metastasis

Contract # C021328
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Albert Einstein College of Medicine

Breast cancer is the leading cancer in women. Understanding the mechanism of breast cancer progression and metastasis is very important in attempts to cure breast cancer. It has been shown that breast tumor-associated macrophages (TAMs) are correlated with a poor prognosis, and that TAMs enhance mammary tumor progression and metastasis in mice. Colony-stimulating factor-1 (CSF-1), a circulating hormone, is the primary regulator of the survival, proliferation and differentiation of tissue macrophages, and regulates the functions of macrophages by binding and activating their cell surface CSF-1Rs. TAMs bear the CSF-1 receptor (CSF-1R) on their surface. The goal is to identify the CSF-1R signaling pathways in TAMs that support mammary tumor progression and metastasis, and to study the function of a newly identified CSF-1R ligand, interleukin-34 (IL-34). There are seven tyrosines (Ys) in CSF-1R, which are phosphorylated upon CSF-1 binding and create binding sites for downstream signaling molecules.

To simplify analysis of the CSF-1R signaling pathways that regulate metastasis, angiogenesis, motility and invasion (MAMI), a system was established that allows for the necessity and sufficiency of particular CSF-1R phosphotyrosine signaling pathways. Necessity was tested by mutating each tyrosine (Y) to phenylalanine (F), and Y721 and Y706 respectively have been shown to enhance and inhibit tumor cell invasion in *in vitro* tumor cell/macrophage co-culture assays. Sufficiency was tested by adding back Ys to CSF-1Rs in which all Ys have been mutated to F, except for Y559 and Y807, which have been shown to be necessary for CSF-1-mediated cell survival and proliferation. Using this Y7F.Y559,807add-back(AB) receptor, Y721 and Y706 were separately added back to test their sufficiency. To ascertain the effects of CSF-1R mutations on tumor progression and metastasis, attempts to establish a cassette-based mouse CSF-1R knock-in strategy are underway.

Initial attempts were unsuccessful, probably because of the region targeted. Targeting another exon is being tried and, as an alternative, using *Csf1r* promoter-driven CSF-1R transgenes on the *Csf1r-/-* background. The existence of a novel CSF-1R ligand, IL-34, may explain the observation that the phenotype of CSF-1R-deficient mice is more severe than the phenotype of CSF-1-deficient mice. Collaborative studies are underway, applying IL-34 gene targeting and transgenic approaches to understand the biology of IL-34, which as preliminary studies demonstrate, is expressed in mammary tumor cells. It is believed that an understanding of regulation by IL-34 will provide new opportunities for the development of additional therapeutic approaches in the treatment of breast cancer.

Checkpoint Functions of the BRCA1/BARD1 Tumor Suppressor

Contract # C021330
Shuang Fu and Richard Baer
Columbia University

The cell cycle checkpoints induced by genotoxic stress are particularly common targets of oncogenic lesions in human cancer. BRCA1 has now been implicated in activation of several cell cycle checkpoints induced by DNA damage, and it is thought that these checkpoints

contribute to the tumor suppression activity of BRCA1. However, the molecular mechanisms by which BRCA1 mediates checkpoint control are not understood. *In vivo*, BRCA1 associates with the BARD1 protein to form a potent E3 ligase that can readily catalyze ubiquitin polymerization. To ascertain whether ubiquitin ligase activity of BRCA1/BARD1 is required for checkpoint control, work is underway to identify its enzymatic substrates and determine the biological consequences of their conjugation to polyubiquitin. In collaboration with Dr. Junjie Chen and his colleagues, it was recently found that BRCA1 ubiquitinates its binding partner CtIP, and that the ubiquitinated CtIP associates with chromatin following DNA damage. Moreover, the enzymatic activity of BRCA1, as well as its ability to bind CtIP, is required for BRCA1-mediated activation of the G2/M cell cycle checkpoint. It was hypothesized that polyubiquitination of CtIP is lysine K6-linked, and that polyubiquitination of CtIP is BRCA1-dependent.

It had been previously shown that BRCA1/BARD1 heterodimers preferentially catalyze formation of polyubiquitin chains through an unconventional isopeptide linkage involving lysine residue K6 of ubiquitin. To ascertain whether BRCA1-mediated ubiquitination of CtIP also generates K6-linked chains, a sensitive assay was developed to detect BRCA1/BARD1-mediated ubiquitination *in vivo*. Cells are cotransfected with expression plasmids encoding ubiquitin polypeptides with a hexahistidine tag, and CtIP with an HA tag. Polyubiquitinated proteins are then purified from cell lysates by affinity chromatography on nickel beads, and the CtIP conjugates are detected by immunoblotting with HA-specific antibodies. Using this system, polyubiquitinated CtIP was detected *in vivo,* and the linkage of their conjugated chains are now in testing using mutant derivatives of ubiquitin that harbor defined amino acid substitutions of their lysine residues.

To confirm that CtIP polyubiquitination is dependent on BRCA1 expression, siRNA technology was used to knock-down BRCA1/BARD1 expression *in vivo*. Cells were then transfected with expression plasmids encoding ubiquitin polypeptides with a hexahistidine tag, and CtIP with an HA tag. The polyubiquitinated CtIP conjugates can be isolated and detected as mentioned above. Conditions for siRNA knock-down have been optimized, and the presence of CtIP conjugates is now undergoing testing in BRCA1/BARD1-depleted cells.

Future directions include studies to: 1) identify the sites of BRCA1-mediated CtIP polyubiquitination; 2) determine the role of CtIP polyubiquitination in cell cycle checkpoint control and DNA repair; and 3) identify other potential enzymatic substrates of BRCA1/BARD1 and ascertain their role in cell cycle checkpoint control.

Influence of RAD9 and RAD9B Proteins on BRCA1

Contract # C021331
Corinne Leloup and Howard B. Lieberman
Center for Radiological Research, Columbia University

BRCA1 and RAD9 are both involved in embryonic development, DNA repair and carcinogenesis. The hypothesis was addressed that RAD9 influences BRCA1 function. BRCA1 activity depends on several factors, including its amount in the cell, its phosphorylation level and possibly its subcellular localization. Under certain circumstances, it appears that BRCA1 migration from the nucleus to the cytoplasm is related to cancer.

It was examined whether expression, location and phosphorylation of BRCA1 are influenced by the presence or absence of RAD9. The same questions were asked about RAD9B, a protein

whose sequence is similar to RAD9's. BRCA1 becomes phosphorylated after irradiation. Therefore, research focused on whether the response of BRCA1 to irradiation is influenced by the levels of RAD9 and RAD9B. Since animal models are useful to study human diseases, the experiments were performed with mice cells.

BRCA1 protein levels were quantified in three different cell populations: wildtype mouse embryonic (ES) cells, as well as mouse ES cells knocked-out for RAD9 or RAD9B. Nuclear and cytoplasmic extracts were purified and run on polyacrylamide gels. The proteins were then transferred to a membrane and probed for BRCA1 with antibodies. Purity of the extract and equal loading of proteins were monitored using an antibody specific for a nuclear protein: HDAC1. Phosphorylation induced a shift in the protein migration pattern. Those measurements were performed in extracts from untreated cells and in gamma-irradiated cells.

The following results were obtained: 1) the level of endogenous BRCA1 in untreated wildtype mouse ES cells is equivalent to its level in ES cells lacking RAD9 or RAD9B; 2) the level of endogenous BRCA1 in irradiated wildtype mouse ES cells is equivalent to its level in ES cells lacking RAD9 or RAD9B; 3) BRCA1 is localized in the nucleus in all cell types, irradiated or not; and 4) irradiation induces a switch in mouse BRCA1 mobility that most probably corresponds to a change in BRCA1 phosphorylation in all cell lines.

Thus, the results of this study suggest that the presence or absence of the RAD9 family of proteins does not have any impact on BRCA1 location, quantity or phosphorylation levels in mouse ES cells. Furthermore, mouse BRCA1 in ES cells behaves similarly to human BRCA1 in regard to localization and response to irradiation.

ARA70 BETA Promotes Cell Proliferation in Breast Cancer

Contract # C021335

Fei Chen, Yi Peng, Hongfeng Guo, Robert Schneider and Peng Lee
Department of Pathology, New York University Medical Center

Androgen receptor (AR)-associated coregulator 70 (ARA70) was first identified as a gene fused to the ret oncogene in thyroid carcinoma and subsequently as a coactivator for AR. ARA70α has also been shown to be an ER coactivator. Two isoforms of ARA70 have been identified: a full-length 70 kDa version termed ARA70α, and an internally spliced 35 kDa variant termed ARA70β. However, ARA70's biological relevance and molecular mechanism in breast cancer have not been well studied. MCF7 and MDA-MB-435 breast cancer cells were established stably expressing ARA70α and ARA70β. It was shown that ARA70β promotes cell proliferation, transformation and invasion in both MCF7 and MDA-MB-435 cells in cell proliferation, anchorage independent assays, as well as Matrigel invasion assays. Further, these enhanced growth and invasion effects were dependent on both androgen and estrogen. Affymetrix oligonucleotides microarray analysis showed dramatically increased MDM4 and decreased p21 levels. These data indicate that ARA70β promotes cell proliferation through the MDM4-P53 pathway in breast cancer. Studies with ARA70α and ARA70β transgenic mice are underway.

Mitochondrial DNA Instability in Breast Tumorigenesis

Contract # C021336
Mariola Kulawiec and Keshav K. Singh
Roswell Park Cancer Institute, Cancer Genetics Department

Mitochondria are the powerhouses of the cell, providing energy by producing energy-rich molecules of ATP through oxidative phosphorylation (OXPHOS). An unfortunate byproduct of OXPHOS is the generation of damaging reactive oxygen species (ROS). Mitochondria contain their own genetic system, a 16,569-bp super-coiled, double-stranded DNA molecule (mtDNA). Due to the close proximity of the electron transport chain (ETC), lack of protective histones and an inefficient DNA repair system, the mitochondrial genome is exposed to the deleterious effects of ROS, resulting in an increased frequency of mtDNA mutations. To understand the role of mtDNA mutations in breast tumorigenesis, comprehensive analysis was conducted of mutations in the mitochondrial genome of different breast cancer cells, revealing that breast cancer cells contain mutations in D-loop control region, ND2, ND5, CoxI, ATP6 and cyt b genes.

Cybrid cell lines were created, which were of identical nuclear background but differed in mitochondrial genome. Two breast cancer cell lines carrying mtDNA mutations were used as a source of mitochondria: MDAMB435 and MDAMB231. The tumorigenic phenotypes of these cells were compared with wildtype cybrids containing mitochondria from platelets of a healthy volunteer. Although these cybrids do not show increased invasiveness, they do show increased proliferation compared to wildtype cybrid cell lines. This study suggests that mtDNA mutations present in these cybrids may contribute to breast tumorigenesis by increasing the rate of cell proliferation. Studies are underway to understand the mechanism of increased proliferation due to mutations in mtDNA.

Stat3 Is Tyrosine-Phosphorylated Through the Interleukin-6/Glycoprotein 130/Janus Kinase Pathway in Breast Cancer

Contract # C021338
Sizhi Paul Gao [1], Marjan Berishaj [1], Simi Ahmed [2], Kenneth Leslie [1], Hikmat Al-Ahmadie [3]
William L. Gerald [3], William Bornmann [4] and Jacqueline F. Bromberg [1]

[1]Department of Medicine, Memorial Sloan-Kettering Cancer Center
[2]Laboratory of Molecular Cell Biology, Rockefeller University
[3]Department of Pathology, Memorial Sloan-Kettering Cancer Center
[4]Division of Experimental Diagnostic Imaging, University of Texas M.D. Anderson Cancer Center

Signal transducer and activator of transcription 3 (Stat3) are constitutively activated in approximately 50 percent of primary breast cancers. A number of different mechanisms responsible for Stat3 activation, including abnormal activation of upstream signals such as Janus kinases (Jaks), have been implicated in breast cancers. Six breast cancer-derived cell lines were examined, expressing high or low levels of activated Stat3, as well as primary breast cancer specimens. A pan-Jak inhibitor P6 treatment resulted in complete abrogation of activated Stat3 and inhibition of cell growth in the cell lines. Jaks are required for cytokine signaling, and glycoprotein 130 (gp130) receptor-associated Jaks are known mediators of Stat3 activation. Blockade of the gp130 receptor or sequestration of gp130 ligand interleukin-6 (IL-6)

led to a decrease in activated Stat3 levels. Conditioned media from those cell lines expressing high levels of activated Stat3 contained IL-6 and were capable of causing Stat3 activation. Furthermore, IL-6 levels were examined in primary breast tumors, and a positive correlation was found between activated Stat3 and IL-6 levels. In summary, it was discovered that a principal mechanism of Stat3 activation in breast cancer occurs through the IL-6/gp130/Jak pathway.

Characterization of Wnt5A Signaling in the Mammary Gland

Contract # C021339
Yutaka Takigawa, Cristina L. Agbunag and Anthony M.C. Brown
Department of Cell and Developmental Biology
Weill Medical College of Cornell University

The Wnt family of secreted signaling factors regulates the development and homoeostasis of numerous mammalian tissues, including the mammary gland, and hyperactivation of Wnt signaling is associated with cancer. Wnt proteins exert their effects via two distinct modes of signaling: the canonical Wnt/β-catenin pathway, and a "non-canonical" mechanism that is independent of β-catenin and less well characterized. Wnt5a is a Wnt protein that is frequently overexpressed in human breast cancer. Unlike the mammary oncogene Wnt1, which acts via the canonical Wnt/β-catenin pathway, Wnt5a mostly signals via a non-canonical mechanism. This mechanism has been associated with tumor cell invasion in some tissues, but it is unclear whether Wnt5a signaling in the breast would promote or antagonize tumor progression.

In order to determine experimentally whether Wnt5a acts as an oncogene or tumor suppressor in mammary tissue, four founder lines of mice were generated containing a Wnt5a transgene under the control of a tetracycline-responsive element (TRE). These mice were crossed with an MMTV-rtTA strain that expresses a tetracycline-dependent transcriptional activator in the mammary gland. The resulting bitransgenic females were treated with doxycycline (Dox), and Wnt5A RNA expression in mammary glands was assessed by quantitative reverse transcriptase-polymerase chain reaction (RT-PCR), showing successful induction of the Wnt5a transgene by Dox. Two lines with the most robust inducible Wnt5A expression were chosen for future analysis of mammary phenotype.

Investigation of the role of Wnt5A in invasive cell motility was also begun. MDA-MB-231 breast cancer cells were infected with a retrovirus expressing Wnt5A, and their behavior analyzed in cell monolayer-wounding assays and transwell migration assays. Preliminary results suggest that Wnt5A suppressed cell motility in both assays. To investigate the mechanistic basis by which Wnt5a affects cell phenotype, the intracellular protein Dishevelled (Dvl) was studied as a key component of the non-canonical Wnt signaling pathway. Wnt5a caused phosphorylation of Dvl in MDA-MB-231 cells but had no effect on β-catenin levels.

These results confirm that Wnt5a activates a non-canonical Wnt signaling mechanism in these cells. Further studies of its phenotypic consequences for mammary cells, in cell culture and *in vivo,* are now in progress.

Stim1 and Orai1 Are Critical for Breast Tumor Metastasis

Contract # C021340
Shengyu Yang, William Gerald, Jillian Zhang and Xin-Yun Huang
Department of Physiology, Weill Medical College, Cornell University

Tumor metastasis is the most common cause of death in breast cancer patients. Currently used chemotherapeutic or monoclonal antibody agents target either cytotoxicity to kill tumor cells or anti-angiogenesis. Therefore, development of therapeutic agents that inhibit breast tumor metastasis is very desirable. To achieve that goal, a better understanding is needed of the molecular components involved in breast tumor cell metastasis. One of the vital steps during tumor metastasis is tumor cell migration, which results in invasion of neighboring connective tissue and entry into lymphatic and blood vessels. The ubiquitous second messenger Ca2+ is one of the critical regulators of cell migration. Store-operated channel is the most important Ca2+ entry mechanism among non-excitable cells. STIM1 and Orai1 were recently identified as the molecular components of store-operated calcium channel. Inhibition of store-operated calcium influx by inhibitor SKF96365 or by STIM1 and Orai1 RNAi inhibited the migration and invasion of breast cancer cells.

Further investigation of the molecular mechanism by which Ca2+ influx controls cell migration revealed that blocking store-operated channel impaired the turnover of focal adhesions. The role of STIM1 and Orai1 in breast tumor metastasis was further studied in animal models. Blocking store-operated channel by STIM1, Orai1 RNAi or SKF96365 significantly inhibited the metastasis of breast tumor cells in mice. Moreover, analysis of the expression of STIM1 and Orai1 revealed that Orai1 was overexpressed in breast cancer tissues as compared to normal tissues from breast cancer patients. Therefore, these data demonstrate that STIM1 and Orai1 are critical for breast tumor metastasis and can serve as targets for an anti-metastasis drug screen.

APPENDIX IX

PUBLICATIONS, PRESENTATIONS AND MEETING ABSTRACTS BASED ON BOARD AWARDS

Grantees continue to make important contributions to breast cancer research and education. During the 2007-2008 reporting period, 14 awardees reported the following publications and presentations in the field as a result of funding from the Health Research Science Board:

C020906 **The Trustees of Columbia University in the City of New York**
Project Title: Novel Vector to Promote Radiosensitivity and Apoptosis in Breast Carcinoma

Lebedeva IV, Emdad L, Su Z, Gupta P, Sauane M, Sarkar D, Staudt MR, **Liu Z**, Taher MM, Xiao R, Barral P, Lee S, Wang D, Vozhilla N, Park E, Chatman L, Boukerche H, Ramesh R, Inoue S, Chada S, Li R, DePass AL, Mahasreshti PJ, Dmitriev IP, Curiel DT, Yacoub A, Grant S, Dent P, Senzer N, Nemunaitis JJ, and Fisher PB. 2007. **"Novel Anticancer Cytokine: Focus on Bystander Antitumor, Radiosensitization and Antiangiogenic Properties, and Overview of the Phase I Clinical Experience."** *Intl J Oncology,* 31(5):985-1007.

C020910 **Columbia University**
Project Title: The Role of PTEN in Mediating Indomethacin Anti-Cancer Activity

Shen WH, Balaiee AS, Wang J, Wu H, Eng C, Pandolfi PP, and Yin Y. 2007. **"Essential Role for Nuclear PTEN in Maintaining Chromosomal Integrity."** *Cell,* 128:157-170.

C020912 **Cornell University**
Project Title: Regulation of Breast Cancer-Related Nuclear Factors by NAD^+

Kininis M, Chen BS, Diehl AG, Isaacs GD, **Zhang T**, Siepel AC, Clark AG, and Kraus WL. 2007. **"Genomic Analyses of Transcription Factor Binding, Histone Acetylation, and Gene Expression Reveal Mechanistically Distinct Classes of Estrogen-Regulated Promoters."** *Mol Cell Biol,* 27:5090-5104.

Wacker DA, Ruhl DD, Balagamwala EH, Hope KM, **Zhang T**, and Kraus WL. 2007. **"The DNA Binding and Catalytic Domains of Poly (ADP-Ribose) Polymerase 1 Cooperate in the Regulation of Chromatin Structure and Transcription."** *Mol Cell Biol,* 27:7475-7485.

Wacker DA, Frizzell KM, **Zhang T**, and Kraus WL. 2007. **"Regulation of Chromatin Structure and Chromatin-Dependent Transcription by Poly(ADP-Ribose) Polymerase-1: Possible Targets for Drug-Based Therapies."** In: Kundu TK, Dasgupta D, eds. Chromatin and Disease. New York, NY: Springer, pp. 45-69.

Zhang T, Berrocal JG, Frizzell KM, Gamble MJ, Krishnakumar R, and Kraus WL. 2007. **"Nuclear NAD^+ Signaling and the Regulation of Gene Expression."** FASEB Summer Research Conference on Chromatin and Transcription, Snowmass Village, CO.

Zhang T, Berrocal JG, Frizzell KM, Gamble MJ, Krishnakumar R, and Kraus WL. 2007. **"Chromatin and Epigenetic Regulation of Transcription."** 26th Summer Symposium in Molecular Biology, Pennsylvania State University, University Park, PA.

C020913 **New York University School of Medicine**
Project Title: In Search for the Ubiquitin Ligase of Cyclin D1, a Key Oncoprotein in Breast Cancer

Busino L, Bassermann F, Maiolica A, Lee C, Nolan PM, Godinho SI, Draetta GF, and Pagano M. 2007. **"SCFFbxl3 Controls the Oscillation of the Circadian Clock by Directing the Degradation of Cryptochrome Proteins."** *Science,* 316(5826):900-904.

C020914 **New York University School of Medicine**
Project Title: Tankyrase 1 and Telomere Function in Breast Cancer and Normal Cells

Canudas S, Houghtaling BR, Kim JY, Cuttonaro L, Dynek JN, Chang WG, and Smith S. 2007. **"Protein Requirements for Sister Telomere Association in Human Cells."** *EMBO J,* 26(23):4867-4878.

Canudas S and Smith S. 2007. **"Molecular Determinants of Sister Telomere Cohesion in Hela Cells."** Presentation: "Telomeres and Telomerase," Cold Spring Harbor Laboratory, Cold Spring Harbor, NY.

C020919 **Memorial Sloan-Kettering Cancer Center**
Project Title: Chemical Synthesis of Erythropoietin

Chen G, Wan Q, Tang Z, Kan C, Krishnakumar R, Hua Z, and Danishefsky SJ. 2007. **"Development of Efficient Methods for Accomplishing Cysteine-Free Peptide and Glycopeptide Coupling."** *Angew Chem, Int Ed*, Vol. 46, 39:7383-7387.

C020920 **University at Buffalo, Department of Social and Preventive Medicine**
Project Title: Vitamin D and Breast Cancer: An Epidemiologic Approach

Moeller SM, Reedy J, **Millen AE**, Dixon LB, Newby PK, Tucker KL, Krebs-Smith SM, and Guenther PM. 2007. **"Dietary Patterns: Challenges and Opportunities in Dietary Patterns Research – An Experimental Biology Workshop."** *J Am Diet Assoc,* 107(7):1233-1239.

Millen AE, Pettinger M, Freudenheim JL, Langer RD, Rosenberg CA, Mossavar-Rahmani Y, Duffy CM, Lane DS, McTiernan A, Kuller LH, Lopez AM, and Wactawski-Wende J. 2008. **"Associations Between Incident Breast Cancer and Geographic Location of Residence in the Women's Health Initiative Observation Study."** Presentation: American Association for Cancer Research, San Diego, CA.

C021327 **Albert Einstein College of Medicine of Yeshiva University**
Project Title: Fragmentation of the Golgi Apparatus in Breast Cancer Cells

Riebeling C and Shields D. **"Caspase-Cleavage of Phospholipase D Alters Its Regulatory Response."** 2007. EMBO Workshop on Membrane Traffic in Secretory Pathway.

Riebeling C, Bourgoin S, and Shields D. 2007. **"Role of Phospholipase D in the Endoplasmic Reticulum Stress Response."** Presentation: ASCB meeting, Washington, D.C.

CO21333 **Mount Sinai School of Medicine**
Project Title: Role of the New Wnt Receptor Ryk in Breast Tumor Progression

Vijayakumar S, Liu G, and Aaronson SA. 2007. **"Role of the Paracrine Acting Wnts in Bone Metastasis Induced by Breast and Prostate Cancer Cells."** Cancer Biology Retreat, Mount Sinai School of Medicine.

C021334 **Mount Sinai School of Medicine, Department of Microbiology**
Project Title: Apoptosis of Breast Cancer Cells: Role of RACK1/CIS and STAT3/Twist/AKT2 Signaling

Zhang W, Cheng GZ, **Gong J**, Hermanto U, Zong CS, Chan J, Cheng JQ, and Wang LH. 2008. **"RACK1 and CIS Mediate the Degradation of BimEL in Cancer Cells."** *J Biol Chem*, 283:16416 – 16426.

C021336 **Roswell Park Cancer Institute**
Project Title: Mitochondrial DNA Instability in Breast Tumorigenesis

Kulawiec M, Safina A, Desouki MM, Still I, Matsui S-I, Bakin A, and Singh KK. 2008. **"Tumorigenic Transformation of Human Breast Epithelial Cells Induced by Mitochondrial DNA Replication."** *Cancer Biology and Therapy,* Volume 7, 1732-1743.

Smirgalia DJ, **Kulawiec M**, Bistulfi GL, Ghoshal S, and Singh KK. 2008. **"A Novel Role for Mitochondria in Regulating Epigenetic Modification in the Nucleus."** *Cancer Biology and Therapy*, Volume 7:1182-1190.

C021338 **Memorial Sloan-Kettering Cancer Center**
Project Title: Characterization of a Novel Jak/State Inhibitor for the Treatment of Breast Cancer

Gao SP*, Berishaj M*, Ahmed S*, Leslie K, Al-Ahmadie H, Gerald WL, Bornmann W, and Bromberg JF. 2007. **"Stat3 Is Tyrosine-Phosphorylated Through the Interleukin-6/Glycoprotein 130/Janus Kinase Pathway in Breast Cancer."** *Breast Cancer Res,* 9(3):R32 (*Co-first authors).

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APPENDIX X

REPORTS TO THE HEALTH RESEARCH SCIENCE BOARD ON PESTICIDE-RELATED ISSUES

A. April 27, 2007 Report

B. October 3, 2008 Report

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Health Research Science Board

April 27, 2007

PESTICIDE-RELATED DUTIES

Survey of State Agencies - Public Health Law 2411(1)

- **(A)** Survey state agencies, boards, programs and other state governmental entities to assess what, if any, relevant data has been or is being collected
  which may be of use to researchers engaged in breast, prostate, or testicular cancer research
- **(B)** Consistent with the survey conducted in (A), compile a list of data collected by state agencies
  which may be of assistance to researchers engaged in breast, prostate, or testicular cancer research

PESTICIDE-RELATED DUTIES – STATE SURVEY (cont.)

- Request for data sets sent to 117 State entities
- Received information on 94 data sets
- Survey includes description of data set, specific types of data included, years, number of records, confidentiality status, format, etc.
- Examples: NYSDOH, NYSDEC, worker EMF database from NY Power Authority, noise levels from NYS Bridge Authority
- Document made available to requestors

PESTICIDE-RELATED DUTIES - REPORTING VS. USE

- The board shall compare the percentage of agricultural crop production general use pesticides being reported to the total amount of such pesticides being used in this state as estimated by Cornell University, Cornell Cooperative Extension, the Department of Environmental Conservation, and the Environmental Protection Agency [PHL §2411(1)(g)]

PESTICIDE-RELATED DUTIES - REPORTING VS. USE (cont.)

- "Reporting" – defined as commercial applicator use and sales to private applicators reported for 1997 under PRL
- "Use" - best available data found to be data from grower surveys done by the U.S. Department of Agriculture (USDA) and New York State Department of Agriculture and Markets (NYSDAM) about pesticide use on fruit
- Selected 9 active ingredients for comparison
- Findings: for 7 of the 9 active ingredients, there was fairly good agreement between reported pesticide sales to private applicators and use on fruit estimated by USDA/NYSDAM

PESTICIDE-RELATED DUTIES – EXPOSURE VS. USE

- Consider, based on evolving scientific evidence, whether a correlation exists between pesticide use and pesticide exposure. As part of such consideration the board shall make recommendations as to methodologies which may be utilized to establish such a correlation [PHL § 2411(1)(f)].

PESTICIDE- RELATED DUTIES - EXPOSURE VS. USE (cont.)

- DOH presentation on exposure assessment
  - focus on factors that influence exposure from pesticide use: applicator, method of application, site of application, frequency of application, application rate
  - discussion of available data for exposure assessment: biological monitoring; environmental sampling; release or use data; production, distribution and sales data
- Document with list of references (abstracts)
  - peer-reviewed journals or government publications
  - studies in which chemical exposure measured in subjects and related to amount of chemical used at time of exposure
  - living document - can add or remove references

DUTY RELATED TO EVALUATION OF THE DATABASE

- Evaluate the basis, efficiency, and scientific utility of the information derived from pesticide reporting and recommend whether such system should be modified or continued (sections 33-1205 and 33-1207 of ECL)
- Addressed in biennial reports (PHL §2413)

WEB PAGE REQUESTS FOR PESTICIDE DATA AT CORNELL WEB SITE, 2002-2006

Directory	2002	2003	2004	2005	2006
Main page	113,000	141,000	152,000	249,000	228,000
1997 data	2100	2900	2200	4800	8400
1998 data	3600	4600	4800	7600	11,000
1999 data	3700	3500	2200	5300	9200
2000 data		3000	1700	4900	8400
2001 data			3600	5000	8800
2002 data			600	5400	8500
2003 data					12,000
2004 data					2700

Numbers are rounded. See handout for notes on 2002, 2003, and 2004 data.

REQUESTS FOR PESTICIDE DATA FULFILLED FOR 1997-2004 DATA

Requestor	Number
DEC – various departments	87
Cornell – various departments	10
DOH, DOH/HRSB	5
EPA, USDA/EPA	3
Total	105*

*Does not include DEC's annual summaries of the data. See handout for description of requests.

DEC Uses for PRL Data

Bureau of Pesticides Management uses PRL Data in their Decision Making Process

Registration Decisions:

(how much was used and where?)

(availability and use of alternatives)

(always a push for new products)

(replacements for less desirable products)

DEC Uses for PRL Data

Groundwater Assessments:

If products are showing up in groundwater, that information is taken into account when making registration decisions.

DEC Uses for PRL Data

Products Labeled **NOT FOR USE** on Long Island:

(match list of registered products with those shipped and used)

(groundwater protection issues)

DEC Uses for PRL Data

Evaluate the Need for Outreach:

(intent to emphasize least toxic alternatives)

DEC Uses for PRL Data

Validate Registrant Claims:

(promises, statements made by registrants in registration negotiations)

(replacement of older products)

(registrant's intention to remove from marketplace)

DEC Uses for PRL Data

Ability to Track NYS Restricted-Use Pesticide Products

(where they are sold and used)

This allows us to cross reference current commercial permit holders with registered NYS restricted-use pesticide products.

DEC Uses for PRL Data

Helps eliminate Inactive Applicators (retired, deceased, etc.)

Gives available information to assist inspectors when responding to complaints

Compare county totals and see increases and decreases from year to year

DEC Uses for PRL Data

Reviewed data to see if there was any correlation with regard to lobster die-off in Long Island and pesticide spraying

DOH USES OF PESTICIDE DATA

- Used for comparison of reporting to DEC and use on fruit as estimated by USDA/NYSDAM
- Assists in answering queries from public
- Assists with pesticide registration issues by providing information on extent of use of certain products

DOH USES (cont.)

- Coram/Mt. Sinai/Port Jefferson (CMP) Investigation
  - Follow-up to breast cancer maps that showed a significantly higher than expected incidence of breast cancer for 1993-1997 (7 ZIP codes)
  - Reviewed known risk factors, including many types of environmental data such as air pollution, water quality, pesticides

DOH USES (cont.)

- Major finding related to pesticides: overall commercial application rates of pesticide products in CMP area were higher than in the rest of Suffolk County

- Environmental Public Health Tracking
  - Data: time and space
  - Indicator

Pesticide Report

October 3, 2008

NEW YORK STATE DEPARTMENT OF ENVIRONMENTAL CONSERVATION

Margaret O'Neil, Chief

Pesticide Reporting & Certification Section

518-402-8748

pestmgt@gw.dec.state.ny.us

DEC Review of Reports

- a) be in the Department's standard format;
- b) contain complete data in every column;
- c) have valid certification numbers or a valid commercial permit number;
- d) be legible;
- e) list the "undiluted" quantity of pesticide used;
- f) list an acceptable "unit of measurement";
- g) list the exact date of application; and
- h) contain complete addresses (including house number and street name, full name of city or village and zip code).

DEC Review of Reports

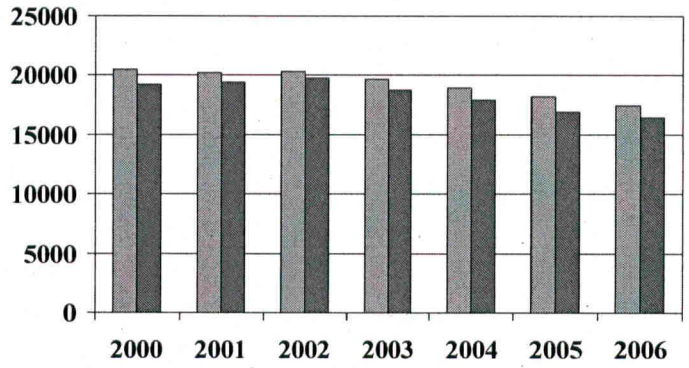
- Automated review
- Error reports
- Outreach
- Corrections to data
- Revise data
- Update report summaries on website

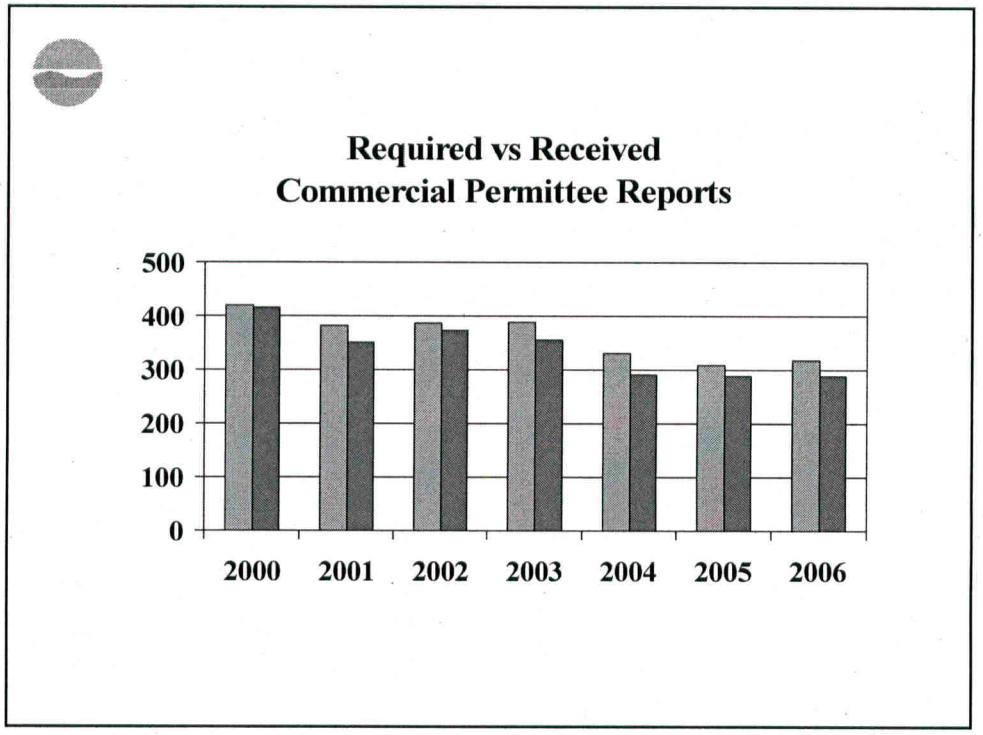
Compliance Rate for Reports

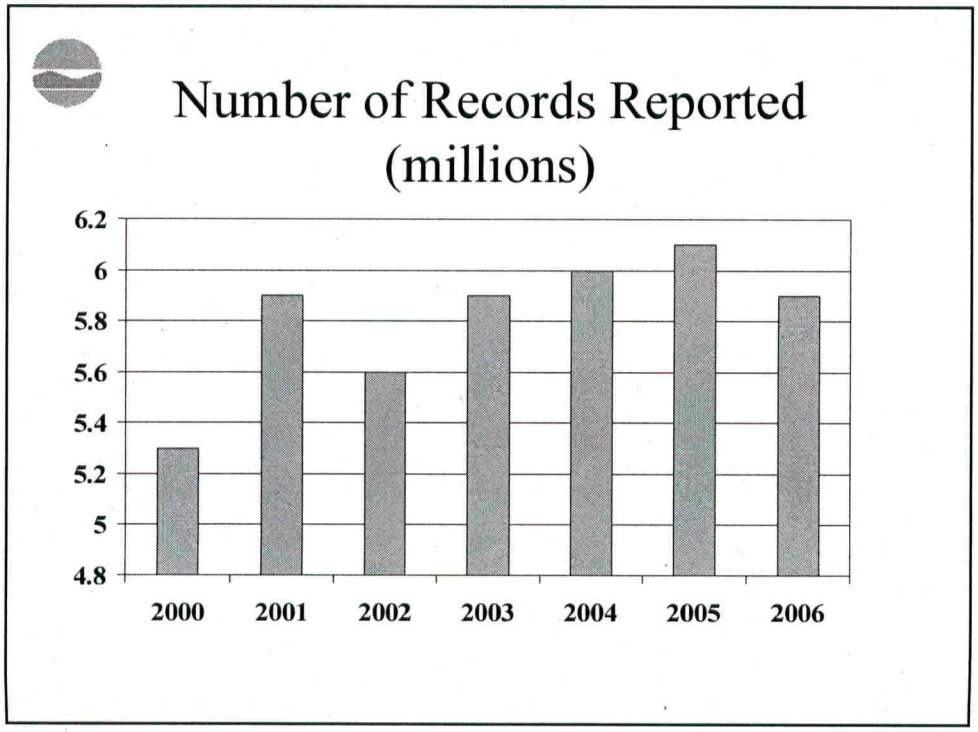
2006: 5.9+ million records
2.9 million GLS and 20.9 LBS
94% APP's and 92% CP's reported

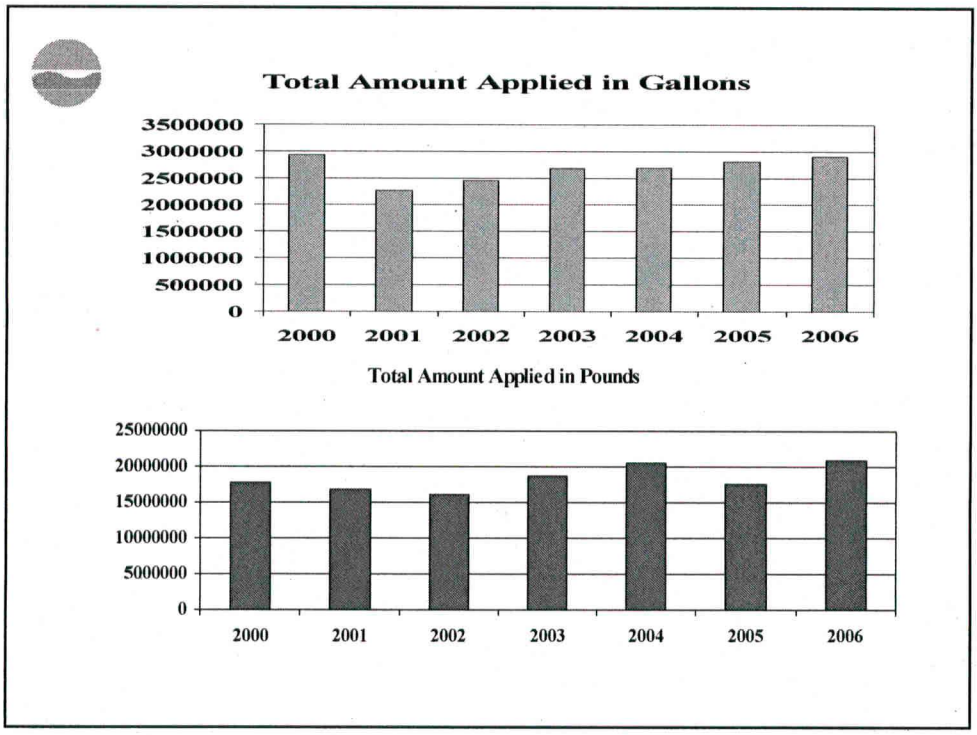
2005: 6+ million records
2.8 million GLS and 17.5 million LBS
93% APP's and 94% CP's reported

Required vs Received Applicator Reports




Required vs Received
Commercial Permittee Reports
500
400
300
200
100
0
2000
2001
2002
2003
2004
2005
2006


Number of Records Reported
(millions)
6.2
6
5.8
5.6
5.4
5.2
5
4.8
2000
2001
2002
2003
2004
2005
2006



Electronic Data

2000: 12%

2001: 22%

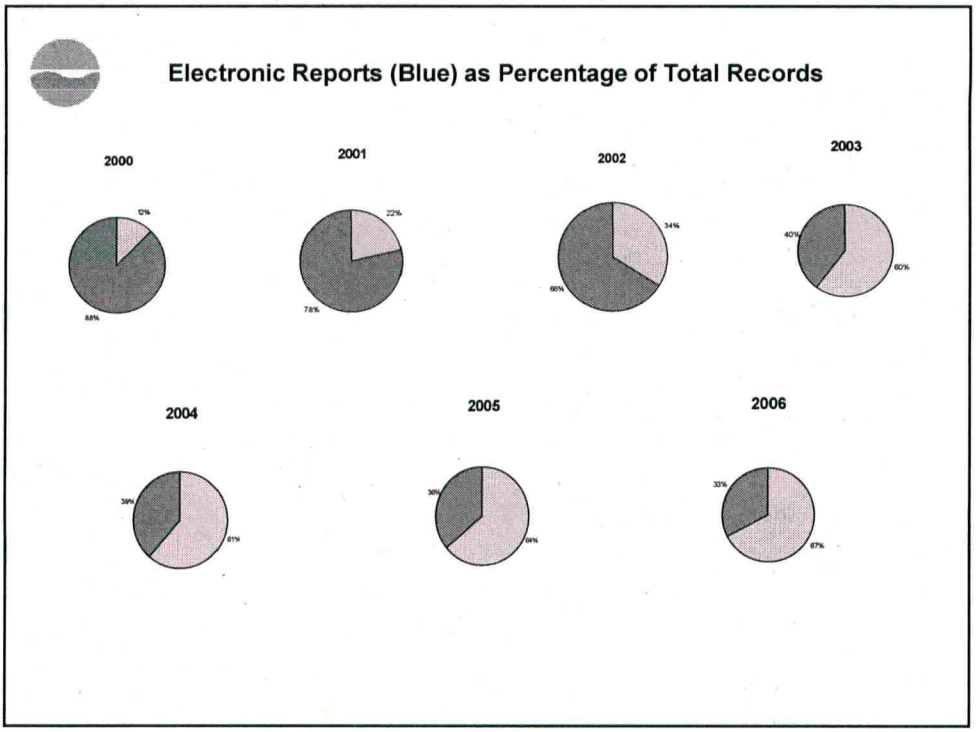
2002: 34%

2003: 60%

2004: 61%

2005: 64%

2006: 67%



Enforcement

Applicators/Technicians/Permittees

- 2006: 1,062
- 2005: 1,393
- 2004: 1,663
- 2003: 1,894
- 2002: 1,437
- 2001: 1,680
- 2000: 2,500

Enforcement (cont'd.)

- Assessed a civil penalty
- Many voluntarily surrender their certification
- No longer certified and cannot make commercial pesticide applications
- Entities who did not settle cannot renew until their violation is resolved

NEW YORK STATE DEPARTMENT OF ENVIRONMENTAL CONSERVATION

THANK YOU

APPENDIX XI

COMMITTEE ON ACCESS TO PESTICIDE REGISTRY AND PESTICIDE APPLICATION INFORMATION

Committee Charge

The Committee is responsible for reviewing requests by researchers for Pesticide Registry information and pesticide application information for use in human health-related research projects. Review and approval of requests shall be consistent with the requirements of Public Health Law Section 2411(1)(d) and with established guidelines to restrict dissemination by researchers of confidential Pesticide Registry or pesticide application information. The Committee shall establish procedures, as necessary, for reviewing the requests in a timely manner, and for forwarding its recommendations to the Health Research Science Board.

The Committee shall make recommendations on the above matters to the full Board for final action.

Committee Membership – December 2008

Representing the Health Research Science Board
Nancy K. Kim, Ph.D. (Chair)
Heather C. Dantzker, Ph.D., Program on Breast Cancer and Environmental Risk Factors, Cornell University
Marc Wilkenfeld, M.D., Columbia University Medical Center

Breast Cancer Advocacy Issues
Mara Ginsberg, To Life!
Erin O'Leary, Ph.D., State University of New York (SUNY) at Stony Brook

Chemical Pesticides and/or Their Environmental Implications
William C. Cooke, Citizens Campaign for the Environment
John P. Hassett, Ph.D., SUNY College of Environmental Science and Forestry
Alan Rabideau, Ph.D., SUNY at Buffalo

Environmental Health Studies
Erin Bell, Ph.D., School of Public Health, SUNY at Albany
Edwin Van Wijngaarden, Ph.D., University of Rochester Medical Center

Commercial or Private Pesticide Application
Jeffrey Williams, New York Farm Bureau
David McMaster, Bartlett Tree Experts
H. Pat Voges, Nassau Suffolk Landscape Gardeners Association

Membership Changes During 2007-2008

Resignations
Philip Landrigan, M.D., M.Sc., Mt. Sinai School of Medicine

Appointments
Heather C. Dantzker, Ph.D., Program on Breast Cancer and Environmental Risk Factors, Cornell University

APPENDIX XII

REQUEST FOR CONFIDENTIAL PESTICIDE REGISTRY OR PESTICIDE APPLICATION INFORMATION
Considered by the Health Research Science Board During 2007-2008

Project Director: Tammo S. Steenhuis, Ph.D.
Department of Biological and Environmental Engineering
Cornell University
Riley-Robb Hall
Ithaca, New York 14853

Project Title: Surveying Upstate New York Well Water for Pesticide Contamination (Cayuga and Orange Counties)

Abstract: The New York State Department of Environmental Conservation (DEC) and others have expressed an interest in conducting a survey of representative areas in upstate New York to determine the occurrence and extent of pesticide contamination in groundwater. Of particular interest are areas of greatest vulnerability where significant pesticide use coincides with shallow aquifers, presenting elevated contamination risks. The results of this survey would contribute to an assessment (by DEC and others) of the human exposure risk from pesticides in groundwater. The first year of work was a pilot-scale program, focused on a single shallow aquifer system in the Cortland Valley, followed by a second year of work in Schenectady County. As discussed in a recent presentation to the HRSB, tasks still underway as part of the Schenectady County project are: 1) analysis of 40 well samples by DEC; and 2) analysis of the correlations between the Pesticide Registry database and the sampling results, which cannot be completed until well water analysis results are available. Data access is requested for work in two counties whose Soil and Water Conservation Districts have agreed to cooperate in this undertaking. This data request is thus for Cayuga and Orange counties.

APPENDIX XIII

STATUS OF AGENCY ACTIONS ON HEALTH RESEARCH SCIENCE BOARD (HRSB) RECOMMENDATIONS FOR PESTICIDE REPORTING 2000 - 2006

SOURCE*	RECOMMENDATION	STATUS
	Recommendations not requiring a change in legislation	
2000(2)	1. Continue to inform researchers of the availability of funds for research on cancer and of the availability of Pesticide Registry data for research.	This is an ongoing effort. The availability of funds continues to be publicized. A Web page describing and providing a link to the Pesticide Sales and Use Database (PSU) is being added to the Department of Health (DOH) Environmental Public Health Tracking Website.
2000(3) and 2006(2)	2. The Department of Environmental Conservation (DEC) should emphasize accurate reporting of Pesticide Registry data by continuing to develop and implement quality assurance and quality control procedures. Incorporate quality checks in the following areas (2006): a. very similar pesticide amounts reported for multiple ZIP codes; b. liquids reported as pounds and solids as gallons; c. quantities reported at county and ZIP code levels that differ by more than an order of magnitude; and d. outliers	This is an ongoing effort of staff from both DEC and Cornell University, who continually seek to improve the reporting rate and data quality by raising the threshold for report acceptance each year. The DOH frontline quality control program to evaluate incoming reports to ensure that basic criteria are met continues to be refined. These criteria were established to maximize the volume of data that can be transferred to the master database. If a report does not meet the criteria, staff seek to reconcile the report with the person filing the report. If the errors are too numerous, the report is rejected and returned to the business or applicator to be corrected and resubmitted. Revised data have been released as a result of these efforts. In addition, in 2006 new computer programs were developed by Cornell to review the data applying the criteria developed and used by DEC in a manual review of the reports. Error reports are produced, and outreach efforts are conducted to correct the data. Once the corrections are made, the revised data are posted on the Website.

*Year of survey from which recommendation originated, with recommendation(s) from the original table.

SOURCE*	RECOMMENDATION	STATUS
2000(4c)	3. Explore strategies to assist the pest control industry with the difficulties of reporting amount of concentrate whenever commercial applicators deal with diluted material.	This is an ongoing educational effort. DEC has conducted extensive telephone outreach on a case-by-case basis educating applicators on correct reporting. In addition, the DEC and Cornell have devised programs to conduct quality checks on reports with quantities that appear to fall outside accepted parameters. Staff review reports containing these "out-of-range" quantities, and the responsible applicators and businesses are contacted. With the approval of the applicator or business, staff correct the reporting errors, and the revised data are posted on the Website.
2000(4d)	4. Explore strategies to assist reporting of locations without street address (e.g., rights-of-way, streams, parks, and aerial applications), such as use of a Geographic Information System (GIS) approach.	This is an ongoing effort. At present, a GIS approach cannot be used for reporting in all areas of the State; some options, such as reporting mile markers, stream tributary numbers, etc., have been implemented, while others are still being explored.
2000(4e)	5. Explore methods to increase or improve reporting, possibly through development of additional outreach, and/or enforcement activities and electronic reporting.	An electronic reporting option is in place and was emphasized at workshops held throughout the State, and by direct mailing to all applicators and sellers. Due to extensive outreach efforts conducted by DEC on a case-by-case basis, more than half of the PSU data are received in an electronic format. However, to mandate electronic reporting would require a legislative change. Enforcement actions are taken each year against applicators and sellers who fail to report.
2002-2003(1)	6. Explore whether the data may be aggregated by different categories, such as use category, different geographical units, etc.	The active ingredient Website contains data aggregated by use category (fungicides, insecticides, herbicides, etc.), as well as Statewide, county, ZIP code or DEC Region.
2006(3)	7. Explore the possibility of making available an application line-item dataset without confidential information for counties and ZIP codes.	DEC will explore the feasibility of a line-item dataset for counties and ZIP codes.

*Year of survey from which recommendation originated, with recommendation(s) from the original table.

SOURCE*	RECOMMENDATION	STATUS
2006(4)	8. Explore the possibility of adding the number of applications to county and ZIP code data.	DEC will explore the feasibility of adding the number of applications to county and ZIP code data.
2006(5)	9. Explore options to include fields from the Pesticide Product Ingredient and Manufacturer System (PIMS), or add the ability to link to PIMS or to the U.S. Environmental Protection Agency Pesticide Product Information System.	This will require major programming changes to the database. There is no funding or staff available at this time to pursue this recommendation.
2006(7)	10. Increase DEC's budget and the funds provided by contract to Cornell.	
	Recommendations that may require a change in legislation	
2006(1)	Allow local health agencies access to the confidential data for surveillance purposes.	Researchers and local health agencies may apply to the HRSB for access to the confidential data. One criterion for releasing the data is that they must be used for human health-related research. Some forms of surveillance may meet the criterion for human health- related research, while others may not. A legislative change would be required to allow local health agencies access to the confidential data without requesting the data from the Board.

*Year of survey from which recommendation originated, with recommendation(s) from the original table.

SOURCE*	RECOMMENDATION	STATUS
	Recommendations requiring a change in legislation	
2000(L1)	1. Change the date by which DEC must issue its report to the Governor and Legislature to allow adequate time for performing quality control and quality assurance on the data. If partial data are released, they should be available as soon as possible; the final report should contain only high-quality data, and the data and report should be readily accessible.	Change in due date requires legislative action. Quality assurance of the data and education outreach for the regulated community are ongoing efforts. All non-confidential data are publicly available on the Internet or by requesting a CD-ROM.
2000(L2)	2. DEC should identify options for including data on pesticides applied by private applicators (primarily farmers) in the database and report on these options to the Board.	Adding these data to the database and reports requires a legislative change.
2000(L3) 2006(L2) and 2006(L3)	3a. DEC should identify options for including in the database data on target organisms and crops to which pesticides are applied, and report on these options to the Board. 3b. Mandate reporting of dosage rate and target organisms. 3c. Include crop/site of application (for those reporting) and crop/site for private applicator sales of general use pesticides intended for agricultural purposes.	Adding these data to the database and reports requires a legislative change.

*Year of survey from which recommendation originated, with recommendation(s) from the original table.

SOURCE*	RECOMMENDATION	STATUS
2000(L4)	4. DEC should identify options for including data on pesticides purchased and applied by private citizens in the database, and report on these options to the Board. DEC should review the upcoming reports from the states of Wisconsin and Oregon, which are currently conducting scoping studies on this issue.	Information from Wisconsin and Oregon has been reviewed. Oregon conducted a pilot survey on household use reporting in 2002, but its entire Pesticide and Use Reporting System was not funded in 2003-2005. The program was funded again in 2006, and the household use survey was implemented. The Oregon 2006 and 2007 annual reports contain information on the survey (see: *http://www.Oregon.gov/ODA/PEST/purs_index.shtml#Annual_reports).* Wisconsin's advisory committee recommended in 2001 that a pilot pesticide use census be conducted, but this recommendation was not implemented because of lack of funding.
2006(L1)	5. Mandate electronic reporting.	An electronic reporting option is in place, and was emphasized at workshops held throughout the State and by direct mailing to all applicators and sellers. Due to extensive outreach efforts conducted by DEC on a case-by-case basis, more than half the PSU data are now received in an electronic format. However, to mandate electronic reporting would require a legislative change.
2006(L4)	6. Revise the requirement for the length of time that commercial applicators, sellers of pesticides, and private applicators must maintain records to not fewer than seven years.	This would require a legislative change. The law currently states that records must be maintained for a period of not fewer than three years.
	Recommendations that have been implemented	
2000(4a)	1. Include a reference to the DOH Pesticide Poisoning Registry Report in the biennial report to the Governor and Legislature.	Done. The biennial report to the Governor and Legislature now includes a reference to the DOH Pesticide Poisoning Registry Report.

*Year of survey from which recommendation originated, with recommendation(s) from the original table.

SOURCE*	RECOMMENDATION	STATUS
2000(4b)	2. Include a reference in the biennial report to the Governor and Legislature to documents for information on the potential for specific pesticides to leach into the groundwater.	Done. The biennial report to the Governor and Legislature includes a reference to documents that provide information on the potential for specific pesticides to leach into the groundwater.
2002-2003(3)	3. Include in the biennial report references to studies that have been stimulated or influenced by the database as examples of how PSU data could stimulate higher-level research.	A list of studies published in the scientific literature that were stimulated or influenced by the PSU data appeared in the 2003-04 biennial report. The list is updated in each subsequent report.
2000(1) and 2006(1)	4. DEC should express data in both pounds of product and pounds of active ingredient.	Done. This requires knowing the specific gravity of every product registered in the State. DEC altered its internal processes to capture this information as products are registered. It has taken several years to capture most of the specific gravities for the 14,000 registered products. DEC made significant progress toward expressing data in both pounds of product and pounds of active ingredient. DEC and Cornell developed a Website that provides active ingredient summaries of the data, starting with year 2003 data.
2002-2103(2)	5. Modify the Websites for ease of use and flexibility in creating reports.	The active ingredient Website has been enhanced with multi-year searching capabilities, and incorporates a number of features that add to the site's usefulness. For example, to facilitate identifying ZIP codes for a search, users can select all ZIP codes contained in or partially contained in a county. In the future, the product-based site will be migrated to this new platform. Documents have been added to the site to assist in pesticide product searches, including frequently asked questions, a data dictionary, and glossary.

*Year of survey from which recommendation originated, with recommendation(s) from the original table.

SOURCE*	RECOMMENDATION	STATUS
2002-2003(4)	6. Explore the possibility of using pesticide-poisoning data in conjunction with the PSU data.	Using pesticide poisoning data in conjunction with PSU data would not be productive since about 99 percent of the pesticide poisoning reports involve improper use of unrestricted pesticides that can be purchased at retail outlets, such as hardware stores and home centers. These products are not included in the PSU database. However, DOH is exploring application of PSU data for environmental health surveillance as part of the Environmental Public Health Tracking Program.
2006(6)	7. Explore options for decreasing the time from a researcher's request for the confidential data to receipt of the data.	The Pesticide Committee modified its process to improve turnaround timeliness by instituting a pre-review process whereby three members of the Committee review the application for sufficient information for the Committee to make an informed decision. Without delaying for scheduling of a committee meeting, staff members work with the applicant to obtain any additional information needed before the meeting.

*Year of survey from which recommendation originated, with recommendation(s) from the original table.

APPENDIX XIV

DOH PESTICIDE SALES AND USE REPORTING OUTREACH LETTER

August 2008

HEALTH RESEARCH SCIENCE BOARD

YORK STATE DEPARTMENT OF HEALTH

Room 500
Flanigan Square
547 River Street
Troy, New York 12180-2216

August 2008

Dear Interested Party:

Information on commercial pesticide applications and some pesticide sales in New York State are available from the Pesticide Sales and Use Reporting Database, which was created by legislation in 1997. The New York State Department of Environmental Conservation receives reports from pesticide applicators and sellers annually; the database is maintained by Cornell University. Much of the data is publicly available. A new search function has recently been added that enhances the utility of the data. Previously, the data were available only by pesticide product, which contains active ingredients and other ingredients. This information is now converted into "pounds of active ingredient." The database can be searched for pesticide products or active ingredients by county, ZIP code, or the entire state on the web at http://pmep.cce.cornell.edu/psur/. In addition, new documents related to the pesticide product searches have been posted to assist users of the data; the documents include Frequently Asked Questions, a data dictionary, and a glossary.

Scientists involved in human health-related research can apply to the Health Research Science Board for access to additional information, including confidential address-specific data. More information for researchers is available at http://www.health.state.ny.us/environmental/pesticide/reporting/ on the New York State Department of Health's website.

We encourage you to visit the web site for the Pesticide Sales and Use Database at http://pmep.cce.cornell.edu/psur/ and to explore the new active ingredient search function and the new information documents. Tell us what you think by completing the survey form at http://pmep.cce.cornell.edu/psur/. Let us know how the database can be made more useful to you. Questions or comments on the Pesticide Sales and Use Database can also be directed to the New York State Department of Health by calling the toll-free information line at 1-800-458-1158 or by e-mailing beoe@health.state.ny.us.

Sincerely,

Nancy K. Kim, Ph.D.
Interim Director
Center for Environmental Health

Staff Support to the HRSB
Nancy K. Kim, PhD • *Phone:* (518) 402-7500 • *Fax:* (518) 402-7509

APPENDIX XV

COMMENTS FROM HEALTH RESEARCH SCIENCE BOARD PUBLIC HEARINGS

A. Comments from April 27, 2007 public hearing

B. Comments from October 3, 2008 public hearing

NYSBCN

New York State Breast Cancer Network
1042 Comfort Road
Spencer, NY 14883
phone: (607) 279-1043 fax: (212) 504-2784
e-mail: nysbcn@earthlink.net

Good afternoon. My name is Susan M. Cohen and I am the chair of the New York State Breast Cancer Network. I am also beginning my 14th year as a breast cancer survivor.

The Network is an organization of more than 20 community-based primarily breast cancer organizations in New York state. We have been in existence now for almost 10 years.

Each year Network member organizations provide support and education services to over 100,000 people affected by breast cancer throughout the state in communities that stretch from Buffalo to Long Island. We focus on all aspects of breast cancer research, prevention, detection, treatment, and policy concerns.

I am going to focus today on only 3 things: 1 global, 1 grounded in the near future, and 1 immediate.

The first point has to do with the Board's seeming to lack a rational funding agenda. The grants that are awarded, for both research and education, appear to be given out piecemeal.

We understand the limitations of the funds that the Board has for this purpose, but some attention should be paid to encouraging grants in particular areas in a coherent way.

We don't have answers to what those areas should be, but other programs do this, such as the Department of Defense's Breast Cancer Research Program and the State of California's Breast Cancer Research Program. No reason exists, really, to keep the Board from starting to work on this through its committee structure so that the committee can make some recommendations to the full Board on how to do this and what areas would be fruitful to focus on.

This leads to our 2nd point, the Board's committee structure. As we know you recognize, revitalization of the Board's committees is vital to its ability to function both efficiently and effectively. We want to encourage the Board to move forward with all due speed to bring those committees back to life and fill them with a diverse set of players from the various stakeholder groups so that the Board can move forward and start to realize its potential for meaningful research and education directed at making a difference, even in small ways, in the struggle to eliminate breast cancer from our lives.

These committees are desperately needed to take a hard look at what the Board has accomplished since it came into being and figure out what has worked and what has not, what needs major overhauling and what needs minor tinkering, what needs new and different approaches and what needs a bit of polishing and refinement, questions like that. Once the hard questions have been asked, the committees need to come up with possible answers and initiatives to solve or at least minimize the problems that have been uncovered or discovered in order to move the Board forward in a functional way.

Essential to the success of these committees is to make sure that the committees that you revitalize have breast cancer survivors on them in sufficient numbers to get some kind of cross section of the breast cancer survivor community—geographically, ethnically, and financially—to accommodate the different needs and perspectives, as well as similar ones, of various survivor groups. This is something that you can do something about without changing the law. All that is needed is an understanding of why this is important and the will to carry it out.

This brings me to our final point, which is the need for advocates not only on these committees but also on the Board itself. We know the Board has no control over who serves on it; this is a matter for the Legislature. We would ask the Board therefore to pass, once again, as it has done on more than one occasion in the past, a resolution asking the Legislature to add additional members to the Board from the breast cancer survivor communities throughout the state, with full voting rights, so that their perspective and experience can be heard and can inform and enrich the discussions and deliberations of the Board in carrying out its mandates under the law that created it.

The legislation behind this represents a law whose time has come; it came within a hair's breadth of passing, having gotten out of committee in the Senate in the final weeks of the legislative center and made it almost to the floor for a final vote. The Assembly had passed the bill earlier in the year. It is only a matter of

time, within the next month this year or at most one more year, before this legislation becomes law.

The legislation is long overdue, and a resolution once again from this Board expressing the need for a diverse group of survivors from across the state, with a vote as well as a voice, to join Ms. Barish in her work would be extremely helpful at this critical juncture in the legislation's history.

Thank you very much for your attention to these 3 concerns. Our member groups look forward to working with you as partners in the future to make the HRSB a truly effective body that can make some small difference to the hundreds of thousands of people affected by breast cancer in New York State every day of the year.

Thank you.

NYSBCN

New York State Breast Cancer Network
1042 Comfort Road
Spencer, NY 14883
phone: (607) 279-1043 fax: (212) 504-2784
e-mail: nysbcn@earthlink.net

Good afternoon. My name is Susan M. Cohen and I am the chair of the New York State Breast Cancer Network. I am also a 15-year breast cancer survivor.

The Network is an organization of 25 community-based primarily breast cancer organizations in New York State. We have been in existence now for 11 years.

Each year Network member organizations provide support and education services to over 100,000 people affected by breast cancer throughout the state in communities that stretch from Buffalo to Long Island. We focus on all aspects of breast cancer research, prevention, detection, treatment, survivorship, and policy concerns.

I last testified before the Board 1½ years ago, on 4/27/07. A lot has happened since then. Our 10-year struggle to change the law to add 6 new breast cancer survivors to the Board, each representing one of the 6 geographic health district areas around the state, and to give at least half of those survivor Board members a vote instead of merely a voice, finally succeeded—and you now have 4 of us appointed to the Board, with another 2 to come sooner rather than later we hope.

We are all hopeful that the huge amount of time and energy we put into this effort over all those years will bear fruit in the coming year, especially when the Board is at full strength, which will hopefully alleviate the problems that the Board has had over the years with reaching a quorum to conduct Board business. On behalf of the Network, we look forward to working with the Board to make it both more functional and more effective.

I would like today to touch upon 3 areas of concern for the Board to examine and work on during the coming year. These involve matters of (1) **policy**, (2) **practice**, and (3) **program**.

The first area of concern is one that I have raised before. It is a **policy** matter and has to do with the Board's seeming **lack of a rational funding agenda** as well as the question of **transparency**.

With respect to the **lack of a rational funding agenda**, the grants that are awarded, for both research and education, appear to be given out piecemeal. We understand the limitations of the funds that the Board has for this purpose, but some attention should be paid to encouraging grants in particular areas in a coherent way.

We don't have definitive answers to what those areas should be, but other programs do this, such as the Department of Defense's Breast Cancer Research Program and the State of California's Breast Cancer Research Program. No reason exists, really, to keep the Board from starting to work on this through its committee structure so that the relevant committee can make some recommendations to the full Board on how to do this and what areas would be fruitful to focus on.

This is particularly important for the coming year since you have more funds than usual at your disposal. As most of you know, this unusual situation resulted from the Board's inability to fund awards this past year because the change in law effectively deprived you of the ability to get a quorum to do so.

The unfortunate consequence of this situation is that you have very few awards that are currently ongoing, depriving you of your traditional practice of inviting funded investigators to present their research to the Board as part of each meeting's agenda. Those of us who try to

attend Board meetings on a regular basis truly miss that always interesting and exciting portion of your meetings, but we look forward to its reinstatement in the future.

A second element of our policy concern implicates **transparency**. I am unable to find a list of proposals, neither scientific nor educational, that the HRSB has funded. Have I simply overlooked such a list—and if so, please tell me where to find it—or does it not exist in a form that the public can access? Its nonexistence—if such is the case—reflects negatively on the Board, yet its absence is easily remedied. I would strongly urge you to give the public some idea of where its money is going.

The need to examine and evaluate the Board's funding policies and strategies leads to our 2nd area of concern, which I have also raised previously and which involves **practice**—namely, **revitalizing the Board's committee structure**. As we know you recognize, revitalization of the Board's committees is vital to its ability to function both efficiently and effectively. We want to encourage the Board to move forward with all due speed to bring those committees back to life and fill them with a diverse set of players from the various stakeholder groups so that the Board can move forward and start to realize its potential for meaningful research and education directed at making a difference, even in small ways, in the struggle to eliminate breast cancer from our lives.

These committees are desperately needed to take a hard look at what the Board has accomplished since it came into being and figure out what has worked and what has not, what needs major overhauling and what needs minor tinkering, what needs new and different approaches and what needs a bit of polishing and refinement, questions like that. Once the hard questions have been asked, the committees need to come up with possible answers and initiatives to solve or at least minimize the problems that have been uncovered or discovered in order to move the Board forward in a functional way.

Essential to the success of these committees is to make sure that the committees that you revitalize have breast cancer survivors on them in sufficient numbers to get some kind of cross section of the breast cancer survivor community—geographically, ethnically, and financially—to accommodate the different needs and perspectives, as well as similar ones, of various survivor groups.

Revitalizing the committee structure is something practical and positive that you can do—all that is needed is an understanding of why this is important and the will to carry it out. I urge you to start to work on that process immediately.

This brings me to our final area of concern, one that I have also talked about in the past, which involves **program**—namely, the **requirements** that you have used for educational RFAs and the **scope** of proposals that are encompassed within each RFA category compared with the scope of proposals that have been funded.

With respect to the **requirements** issue, although we fully understand the need for professional input and assessment to ensure that an educational proposal incorporates sound research principles, we fear that the requirements may be unnecessarily burdensome for many community-based-organization applicants. We urge you to take a look at these requirements, re-assess the degree to which they are necessary, and determine whether their purpose could be achieved in less onerous ways.

In addition, we would ask you to examine the **scope of proposals** funded to date—both scientific and educational—and analyze their content compared to the **scope of activities and research issues** that one could investigate to see if the full range of possibilities are being addressed or if these proposals are falling into narrowly constricted categories. The answers may indicate a lack of breath of coverage, an excessively narrow conception of the purpose of the RFAs, an overly restrictive way of judging the proposals, and/or any number of other explanations, depending on the results. Such an analysis may well point to ways of changing how the HRSB thinks about these things and/or implements them in order to make these awards more relevant, more focused, and more meaningful.

Thank you very much for your attention to these concerns. Our member groups look forward to working with you as partners in the future to make the HRSB a truly effective body that can make some small difference to the hundreds of thousands of people affected by breast cancer in New York State every day of the year.

Thank you.

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