CDMRP
Department of Defense

Breast Cancer Research Program





U.S. Army Medical Research and Materiel Command

Congressionally Directed Medical Research Programs

HISTORY

The Office of the Congressionally Directed Medical Research Programs (CDMRP) was created in 1992 from a powerful grassroots effort led by the breast cancer advocacy community that resulted in a congressional appropriation of funds for breast cancer research. This initiated a unique partnership among the public, Congress, and the military. Since then, the CDMRP has grown to encompass multiple targeted programs and has received more than $6.5 billion in appropriations from its inception through fiscal year 2011 (FY11). Funds for the CDMRP are added to the Department of Defense (DOD) budget, in which support for individual programs, such as the Breast Cancer Research Program (BCRP), is allocated via specific guidance from Congress.

APPLICATION REVIEW PROCESS

The CDMRP uses a two-tier review process for application evaluation, with both tiers involving dynamic interaction among scientists and disease survivors. The first tier of evaluation is a scientific peer review of applications measured against established criteria for determining scientific merit. The second tier is a programmatic review conducted by the Integration Panel (IP), which is composed of leading scientists, clinicians, and consumer advocates. The IP compares applications to each other and makes recommendations for funding based on scientific merit, portfolio composition, and relevance to program goals.

Breast Cancer Research Program

ABOUT THE PROGRAM

Since the BCRP was established in 1992, the dedicated efforts of breast cancer advocates have resulted in more than $2.6 billion in appropriations to the program, including $150 million in FY11. The BCRP vision is adapted yearly to facilitate rapid change and to ensure that the program remains responsive to what is currently happening in the research community. The BCRP has created and introduced unique mechanisms to support a broad portfolio of research and training awards that have transformed the breast cancer field. The BCRP challenges scientists to pursue high-risk research that has the potential to make major leaps forward in breast cancer. The program is committed to supporting new, innovative ideas that reflect the most recent discoveries in the field and could lead to breakthroughs. The BCRP training and early-career awards have provided the foundation for many of today's leading breast cancer researchers, and the program continues to invest in the future generation of breast cancer experts. Recognizing the need to promote team science, the BCRP also created unique award mechanisms that foster synergistic, multidisciplinary partnerships among scientists and consumer advocates.

VISION

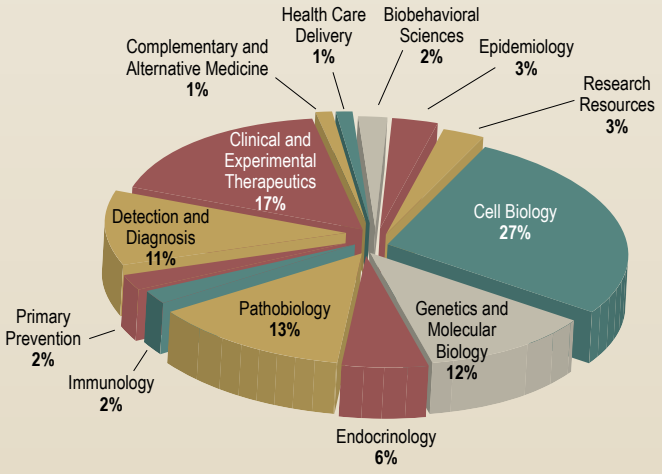
To eradicate breast cancer by funding innovative, high-impact research through a partnership of scientists and consumers.

Through its award mechanisms and innovative approaches, the BCRP plays a leading role in the breast cancer research community.

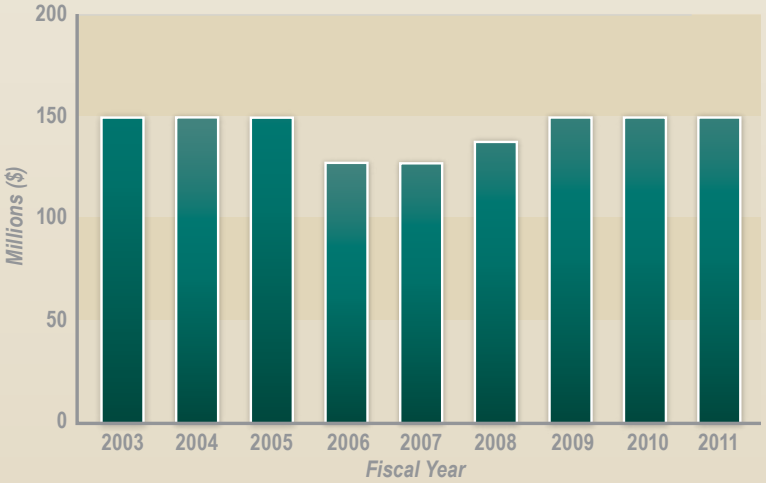
INVESTMENT GOALS

- Encourage innovation and stimulate creativity
- Support research with high-impact potential
- Facilitate synergistic and multidisciplinary collaborations
- Bring new investigators into the breast cancer field
- Train investigators for a career in breast cancer research
- Encourage research in understudied topic areas

FY92–FY10 BCRP Portfolio



Recent BCRP Funding History



Funding for FY92–02 was $1.35 billion.

Strategic Partnerships:

Consumer advocates and scientists working together to eradicate breast cancer

Did you know...

- **Since FY93, consumer advocates have participated in designing the BCRP's program priorities and funding opportunities**
- **Since FY93, consumer advocates have participated as equal voting members in making funding recommendations during programmatic review**
- **Since FY95, consumer advocates have participated as equal voting members in scientific peer review panels**
- **To date, over 3,400 scientists and 700 consumers have contributed their expertise to the BCRP two-tier review process**

The BCRP is widely recognized as a model biomedical research program, and meaningful partnerships have been the foundation of the program's successes from the very beginning. Through this program, the integrated efforts of many dedicated individuals foster unique opportunities in breast cancer research. The two-tiered review process established by the BCRP brings together the expertise of scientists with the perspectives and experiences of consumer advocates. This innovative approach, which has since been adopted by other funding organizations, is an effective way to evaluate research applications for their potential to meet the program's goals.

The BCRP has also enabled partnerships through team-oriented award mechanisms, in which scientists and consumer advocates work together to establish project goals and collaborate on the design and implementation of innovative research.

"The DOD BCRP is a unique collaboration and partnership between scientists and advocates, harnessing the best skills and insights of both to end breast cancer. Educated consumer advocates are involved at every stage of the decision-making process—a very unique aspect of this program. The DOD BCRP promotes innovative, high-impact models of research to make a real difference in ending breast cancer. The DOD BCRP challenges the status quo and encourages new ideas and collaborations, all with a sense of urgency."

Pat Haugen
South Dakota Breast Cancer Advocacy
FY11 Integration Panel Chair

"The BCRP is focused on fostering and supporting cutting-edge breast cancer research that is *impactful*. We recognize, even embrace, the realization that breast cancer is a highly complex disease, and therefore demands strategies that are truly collaborative and interdisciplinary. Active participation of the advocacy community holds our feet to the fire to ensure that each project will have meaningful clinical/translational potential."

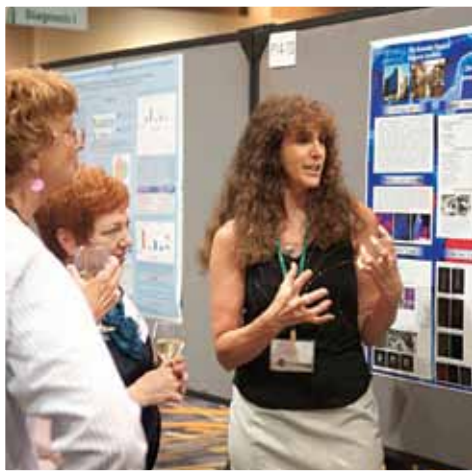
Mark Pegram
University of Miami
FY12 Integration Panel Chair

2011 Era of Hope Conference

On August 2-5, 2011, more than 1,400 researchers, clinicians, and breast cancer advocates participated in the BCRP's sixth Era of Hope Conference in Orlando, Florida. This conference showcases the advances funded by the BCRP. Recognized as one of the premier breast cancer research conferences in the United States, Era of Hope is unique in that it fosters an atmosphere for collaborative thinking and encourages scientists, clinicians, and breast cancer advocates to join forces to challenge paradigms, push boundaries, and identify innovative, high-impact approaches for future research.

The Era of Hope plenary sessions featured thought-provoking topics to stimulate new ways of thinking. The conference opened with "The State of the Science" that provided a comprehensive overview of current breast cancer science, treatment, epidemiology, and the patient experience presented by renowned scientists and advocates. The participants were encouraged to think outside the box during an unorthodox plenary session entitled "Success Models: What Can We Learn?" which featured research and treatment successes of HIV and HPV. Other plenary sessions examined current, groundbreaking information about risk and prevention, non-mutational causes of breast cancer, and the cutting-edge research and innovative individuals that are funded by the BCRP. This Era of Hope conference included a Controversy session, during which panelists and the audience debated "Setting the Bar" – that is, what criteria should be used to measure progress in research.

New for this year's conference were the Lunchtime sessions that provided interactive opportunities for attendees to learn the basics about breast cancer topics in which they may have limited expertise or experience. Basic scientists could attend "Clinical Overview of Breast Cancer," featuring a clinician and a breast cancer advocate relaying the clinical considerations and patient experience during diagnosis and treatment of primary breast cancer. The "Course and Treatment of Metastatic Disease" session featured an advocate living with metastatic disease and a clinician relaying her experience in treating metastatic patients.



For more information about the 2011 Era of Hope conference, including abstracts and videos, visit the CDMRP website at http://cdmrp.army.mil/bcrp/default.shtml

"As I walked through the poster sessions in August 2011 at the Era of Hope, it became clear to me that there is an enormous amount of talented researchers who care greatly about solving the mysteries of a disease that has impacted—and taken—so many lives."

Mary Ann Bopp
Consumer Advocate
Breast Cancer Options

"My participation in the 2011 Era of Hope conference was unexpectedly fruitful. It led directly to my being recruited as an advocate on a new breast cancer research applications with a scientist. When you are open to challenges, you never know what amazing things are in your future."

Bianca Lundien Kennedy
Consumer Advocate
Y-ME National Breast Cancer Organization

Poster Contest

The BCRP held its first Distinguished Predoctoral and Postdoctoral Poster Awards competition at the 2011 Era of Hope Conference. This competition was open to recipients of FY07–FY09 Predoctoral Traineeship, Postdoctoral Fellowship, Multidisciplinary Postdoctoral, and Era of Hope Postdoctoral Awards. A total of 174 individuals entered the competition, and 11 predoctoral and 6 postdoctoral trainees were selected as winners of the Distinguished Poster Awards based on the scientific merit of their abstracts and the quality of their poster presentations. The scientific excellence of these research projects on breast cancer is a testimony to the awardees' dedication to the BCRP's goal of eradicating breast cancer.

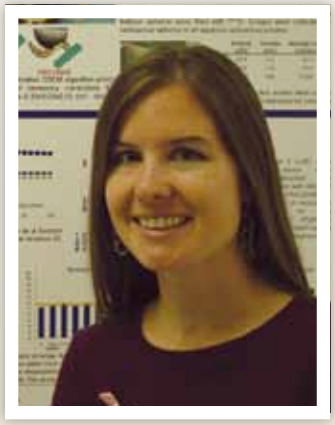
Top Row: Rebecca Lock, Sreejith Janardhanan Nair, Binoj Chandrasekharan Nair, Genevieve Deblois, Pezhman Foroughi
Logo Row: Arne Vandenbroucke, Adam de la Zerda
Third Row: Jenean O'Brien, Johann Bergholz, Gene Bidwell, Richard Ahn, Michele Hickey
Bottom Row: Kevin Knower, John Albeck, Anguraj Sadanandam, Lakshmi Sampath, Jonathan Chou

"Era of Hope is a truly inspiring forum where crucial work was presented and where numerous new collaborations were made. It was a rewarding, gratifying experience to serve as a co-chair with Dr. Vicky Seewaldt. As we began planning our symposium, we immediately found shared perspectives and priorities and agreed that we wanted a thought-provoking session, focusing on both the successes we've had to date in prevention, as well as what we all need to do as investigators and advocates to move forward, 'think out of the box,' and perhaps change our perspectives to get to the answers in preventing primary and metastatic breast cancer. As we got to know each other, it struck me that our experience co-chairing our session represented so much of what is unique and crucial about the BCRP, in bringing scientists and advocates together to set the priorities and truly move the science forward to ending breast cancer."

Debra Madden
Consumer Advocate
Ann's Place, The Home of I CAN

The 2011 Era of Hope conference featured more than 1,100 abstracts focusing on BCRP-funded research. There were nearly 550 organizations represented at the conference, including nearly 150 consumer advocate organizations.

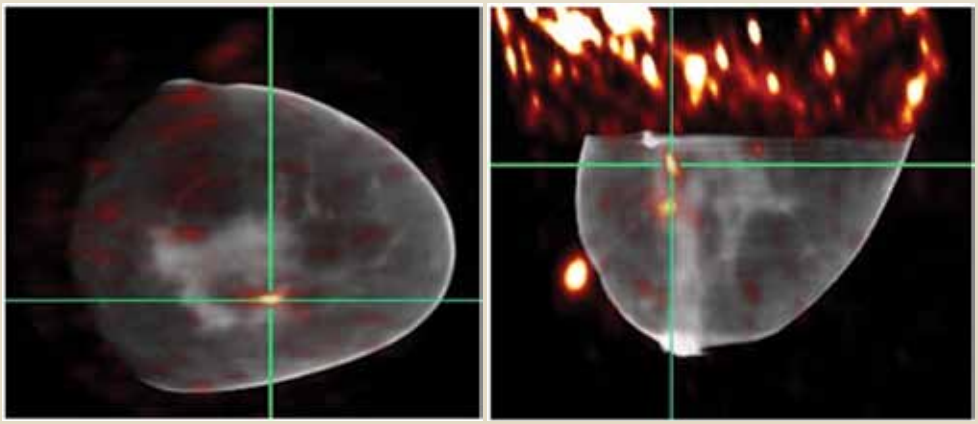
Investing in the next generation of innovators



Whole-Breast Quantification with Dedicated Molecular SPECT-CT Imaging

Kristy L. Perez, Duke University
FY07 Predoctoral Traineeship Award

Mammography, the most common method for breast cancer screening, uses low energy X-rays to detect abnormal masses and/or microcalcifications within the breast. Although mammograms are widely used, the procedure is often inaccurate: studies have shown that mammograms have a false positive rate (i.e., overdiagnosis) of 7%–15%, resulting in unnecessary biopsies and treatment and a false negative rate (i.e., missed cancers) of 10%–30%. Inaccurate detection is especially problematic in younger women whose dense breast tissues can mask malignant lesions. To overcome some of the limitations associated with mammography, Dr. Kristy L. Perez, under the mentorship of Dr. Martin Tornai, investigated the use of molecular single-photon emission computed tomography-computed tomography (SPECT-CT) for accurate early detection of breast cancer. Unlike conventional mammograms, SPECT-CT measures radiotracer (radionuclide) uptake of tumors to distinguish breast tissue function and structure and any tumors present, regardless of breast tissue density. With support from this training award, Dr. Perez demonstrated that SPECT-CT can be used to monitor the spatial localization of radiotracer uptake in the whole breast, potentially providing a stratification of normal, atypical, and premalignant status of the tissues in whole-breast phantoms of various sizes. The ability to quantify the radiotracer uptake was not dependent on breast size or shape. When the whole breast quantification method was retrospectively applied to human volunteer breast data, uptake of the radiotracer could be measured in ductal carcinoma in situ. To confirm these results, the next stage of research will be to acquire more information about the normal tissue radiotracer uptake in human subjects.

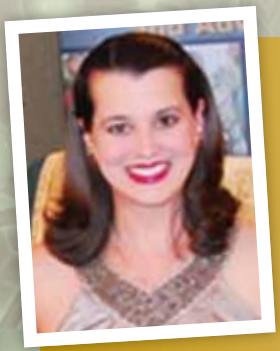


Fused SPECT and CT images of the volunteer's right breast shown in the indicated slice orientations. SPECT images show a clear signal enhancement (indicated at the intersection of the green hashmarks) underneath her biopsy clip, seen near the top of the breast in the transverse CT image slice.

Arsenic Trioxide Loaded Nanobins for the Treatment of Breast Cancer

Richard Ahn, Northwestern University
FY07 Predoctoral Traineeship Award

Current chemotherapeutic strategies cannot distinguish between cancer cells and rapidly growing normal cells, causing toxicity and side effects. Dr. Richard Ahn and colleagues in the laboratory of his mentor Dr. Thomas O'Halloran developed a novel nanoparticulate formulation of chemotherapeutics encapsulated in nano-sized lipid-based drug carriers called nanobins. The objective of designing nanobins was to augment drug pharmacokinetics, improve tumor penetration, and increase therapeutic efficacy. When injected, the nanobins passively accumulate in tumors due to the "leaky" structure of tumor blood vessels. As part of his Ph.D. dissertation, Dr. Ahn developed nanobins loaded with the drug arsenic trioxide (ATO), a chemotherapeutic that is effective at treating certain leukemias, but has been ineffective in treating solid tumors. In mouse models of triple-negative breast cancer, the nanobin-encapsulated ATO demonstrated promising therapeutic efficacy while free ATO had no tumor inhibitory effect. Moreover, the ATO-nanobin therapy was well tolerated without significant systemic toxicity or accumulation in healthy tissues. The researchers conjecture that the ATO-nanobins' sustained antitumor effects may be due to several factors, including its ability to continuously release the ATO within the tumor without the high toxicity associated with free ATO. Based on these exciting findings, Dr. Ahn and colleagues plan to conduct further characterization studies in the hopes of bringing ATO-nanobins to the clinic for treating breast cancer and other solid tumors.



"My decision to participate as a Consumer Reviewer for the DOD Breast Cancer Research Program has proven to be one of the best decisions of my life. It has afforded me the opportunity to take all of the negativity of going through breast cancer and turn it around and harness it into a positive energy, which is focused on making a substantive difference in the breast cancer community. It has been a transformative experience for me."

Bianca Lundien Kennedy
Consumer Advocate
Y-ME National Breast Cancer Organization

Tumor Suppressor Loss and Mitotic Check Point Overactivation as a Crossroads to Cancer

Juan Manuel Schvartzman, Cornell University, Weill Medical College
FY07 Predoctoral Traineeship Award

Understanding the mechanisms of cancer initiation is critical in identifying new drug targets. Previous studies have demonstrated that chromosome instability can initiate cancer. Dr. Juan Manuel Schvartzman, mentored by Dr. Robert Benezra, investigated the molecular mechanisms of breast cancer tumorigenesis resulting from chromosome segregation during cell division. Inactivation of tumor suppressor genes in the retinoblastoma (Rb) pathway is a key event in the development of chromosome instability. Mad2 is an essential component of the cell division checkpoint whose levels are frequently upregulated in breast cancer and other solid tumors. Dr. Schvartzman investigated how the mechanistic relationship between Mad2 hyperactivation and inhibition of the Rb pathway leads to breast cancer tumorigenesis. The study results indicated that overexpression of Mad2 as a result of Rb pathway inactivation leads to chromosome instability. Interestingly, reduction of Mad2 expression in a breast cancer mouse model resulted in delayed breast cancer tumor onset, lower tumor burden, and decreased metastatic potential. Dr. Schvartzman's research findings suggest that Mad2 is an essential mediator of chromosome instability and a novel drug target to inhibit breast cancer initiation. These results were featured on the cover of the June 14, 2011, issue of the journal *Cancer Cell*.

Chemokine-Mediated Breast Cancer Progression and Metastasis

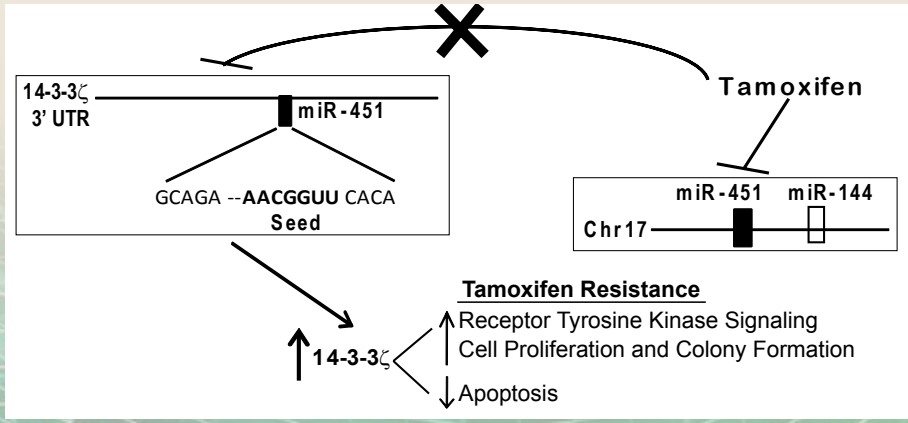
Swarnali Acharyya, Memorial Sloan-Kettering Cancer Center
FY08 Era of Hope Postdoctoral Award

Chemokines are small inflammatory proteins implicated in several normal and disease processes, including cancer. The chemokine family is composed of four groups, distinguished by the spacing of their cysteine residues. The functional role of chemokines in breast cancer remains elusive. CXC chemokines are secreted by aggressive breast cancer cells and are thought to foster tumor growth by enhancing angiogenesis and recruiting various immune and stromal cells to the tumor microenvironment, as well as priming breast cancer cells for metastasis. Mentored by Dr. Joan Massagué, Dr. Swarnali Acharyya is investigating the molecular mechanisms of tumor microenvironment interactions in response to tumor-derived CXC chemokines, and how these interactions promote the growth and dissemination of breast cancer. The investigators found that the chemokines CXCL1 and CXCL2 (CXCL1/2) were highly expressed in a cohort of estrogen receptor-negative (subtype associated with a high risk of lung metastasis) primary breast cancer patient samples. Results from animal models indicated that CXCL1/2 promote both primary breast tumor growth and lung metastases by recruiting specific myeloid cell types to the tumor microenvironment. Inhibition of CXCL1/2 in breast cancer models resulted in significant reduction in primary tumor volume and lung metastasis. These results indicate that CXCL1/2 are promising molecular targets for suppressing breast cancer metastasis.

Overcoming Tamoxifen Resistance in Breast Cancer

Anna Bergamaschi, University of Illinois, Champaign-Urbana
FY08 Postdoctoral Award

As a targeted disruptor of estrogen receptor (ER) signaling in the breast, tamoxifen has played a major role in reducing breast cancer mortality. Unfortunately, many tumors eventually develop resistance to tamoxifen by mechanisms that are poorly understood. Dr. Anna Bergamaschi is investigating a new dimension of tamoxifen activity. As shown by her mentor, Dr. Benita Katzenellenbogen, tamoxifen preferentially upregulates a number of genes in ER+ breast cancer cells that are not regulated by estradiol or other selective ER modulators. Among these is 14-3-3ζ, a member of a highly conserved family of signal transduction proteins that is frequently overexpressed in patients with a poor clinical response to tamoxifen. Dr. Bergamaschi explored the role of tamoxifen in modulating 14-3-3ζ expression. She found that tamoxifen downregulates microRNA451 (miR-451), resulting in the increased expression of 14-3-3ζ, with concomitant increase in expression of survivin, aurora kinase B, and polo-like kinase I, all involved in cytokinesis and mitosis. Overexpressing miR-451 led to decreased 14-3-3ζ, suppressed cell proliferation and colony formation, increased apoptosis, and importantly, restoration of tamoxifen efficacy. These results suggest that miR-451 may have beneficial therapeutic effects in reversing tamoxifen resistance in breast cancer.



"The BCRP is essential to the breast cancer community. Participating as a consumer reviewer for the BCRP is about meaningful contribution to the review process—it is a process that advocates worked hard to develop and implement and continues to sustain. Serving as a BCRP consumer reviewer allows informed advocates to put to considerable use their knowledge and experience and shed light on the impact that research could have on the patient/consumer experience. Advocates at the table do their fair share of groundwork and review to serve as equal participants in the review process with scientists, where informed and relevant decisions are made together."

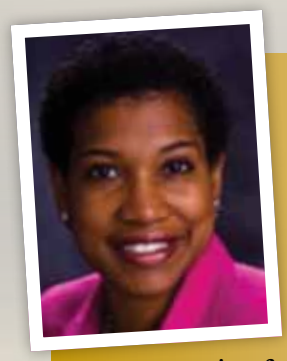
Linda Dias
Consumer Advocate
Annie Appleseed Project

Exploring the Role of HER3 in Breast Cancer

Joan Garrett, Vanderbilt University Medical Center
FY09 Postdoctoral Fellowship Award

The family of epidermal growth factor receptors (EGFR), including HER2 and HER3, plays an important role in breast cancer via tyrosine kinase-activated cell signaling. Therapies targeted to HER2, such as trastuzumab, are often effective, but patients eventually develop resistance to these therapies. To understand this resistance and how to counteract it, Dr. Joan Garrett is focusing on another EGFR family member.

Working with her mentor, Dr. Carlos Arteaga, Dr. Garrett demonstrated that while the tyrosine kinase inhibitor lapatinib inhibited the activity of HER2 and shut down the PI3K/Akt pathway, there was concomitant overexpression of HER3. She found that PI3K/Akt normally represses the activity of a transcription factor required to synthesize HER3 mRNA. By inhibiting PI3K/Akt, lapatinib frees HER3 from this repression, causing HER3 to be overexpressed. Under conditions of excess HER3, there is sufficient binding between HER2 and HER3 to phosphorylate HER3, leading to activation of the PI3K/Akt pathway and tumor progression. Preventing HER2:HER3 binding via trastuzumab diminished the levels of phosphorylated HER3. This provides a mechanistic explanation for recent encouraging clinical trials of combined trastuzumab and lapatinib therapy. Dr. Garrett further showed that inhibition of HER3 with siRNA or a neutralizing HER3 antibody sensitized HER2+ breast cancer cells and xenografts to lapatinib both in vitro and in mouse models. These findings suggest that effectively repressing HER3 should increase the efficacy of lapatinib treatment.



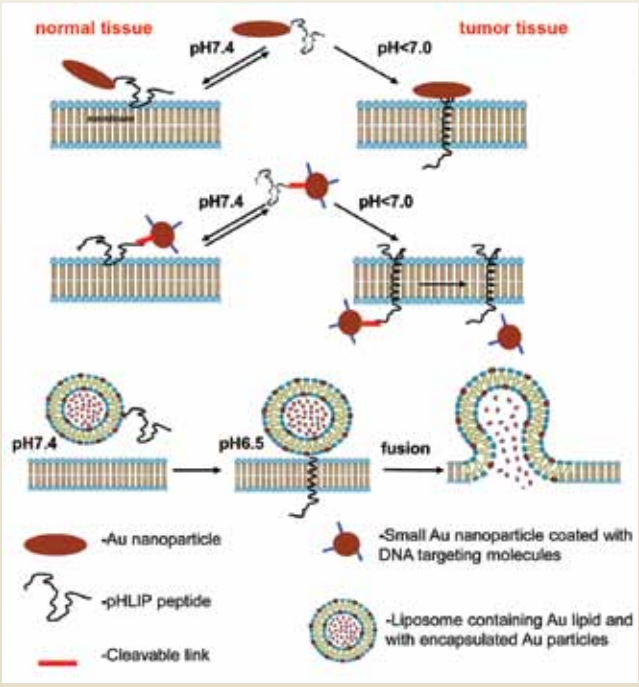
"As a breast cancer survivor and advocate, it does not get much more rewarding than serving as a consumer reviewer for the BCRP. Having a seat at the table of potentially groundbreaking science that could accelerate the eradication of breast cancer is beyond meaningful. Moreover, the camaraderie—the network of strength and support—you share with not only other survivors, but incredible scientists as well, is priceless. It is indeed a remarkable experience."

Joya Delgado Harris
Consumer Advocate
Y-ME National Breast Cancer Organization

Pursuing innovative ideas and new paradigms

Self-Guided Gold Nanoparticles to Target Breast Tumors

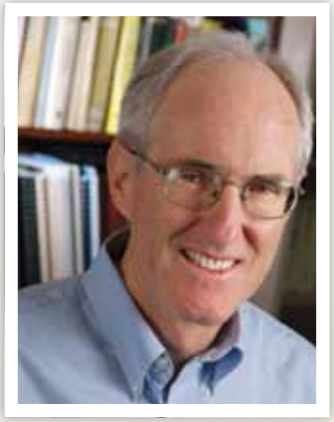
Oleg A. Andreev, University of Rhode Island
FY06 Idea Award



The microenvironment of malignant tumors is significantly more acidic than that of normal tissues. Rapid cellular growth and elevated metabolism of cancer cells give rise to acidosis and hypoxia within the tumor, both of which are thought to foster tumor progression, metastasis, and treatment resistance. Taking advantage of these unique features, Dr. Oleg Andreev developed the pH low insertion peptide (pHLIP), which is a peptide capable of inserting itself into the cellular membrane at acidic extracellular pH levels found in tumors. At neutral pH (i.e., pH found in healthy tissue), the peptide binds weakly to the cell surface without insertion; at acidic pH, pHLIP inserts into the cellular membrane. Dr. Andreev demonstrated that pHLIP can deliver and accumulate a variety of materials, such as nanoparticles and liposomes, specifically at the tumor. For example, when pHLIP-conjugated gold nanoparticles were intravenously injected into mice carrying breast cancer xenografts, the nanoparticles predominantly accumulated in the cellular membrane of cancer cells without significant side effects. Currently, Dr. Andreev is assessing whether the nanogold-pHLIP constructs can be used as agents for tumor-specific optical radiation thermotherapy.

"I have taken a diagnosis of breast cancer and turned it into a force that is now enabling me to make a difference in identifying future treatments, promising researchers, and possibly a cure. Being a consumer reviewer provides me that opportunity to give back to the breast cancer community."

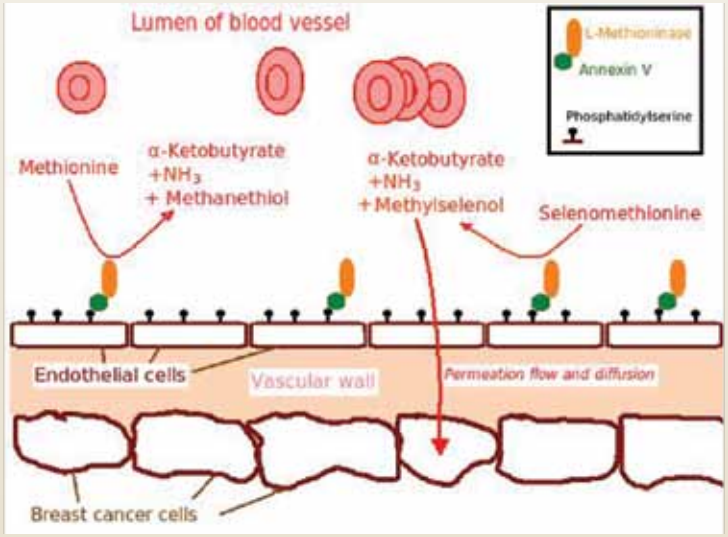
Mary Ann Bopp
Consumer Advocate
Breast Cancer Options



New Enzyme Prodrug and Methionine-Depletion Combination Therapy of Breast Cancer Designed for Effective Delivery to the Tumor

Roger Harrison, University of Oklahoma
FY07 Idea Award

Dr. Roger Harrison is developing an innovative dual-action therapeutic with the potential to overcome the side effects and dose-limited toxicity that is common to chemotherapies. The novel therapeutic utilizes a selenomethionine prodrug along with an L-methioninase-annexin V fusion protein for the treatment of breast cancer. It is designed to specifically target breast cancer cells through annexin V binding to phophatidylserine molecules, which are expressed on the external surface of tumor blood vessels. The L-methioninase enzyme will convert the selenomethionine prodrug to the active form, methylselenol, which generates toxic oxygen radicals, causing tumor cell death. L-methioninase will concomitantly degrade the amino acid methionine, thus starving tumor cells of this essential amino acid. In cell-based in vitro studies, the L-methioninase-annexin V fusion protein demonstrated strong and specific binding to endothelial cells. Furthermore, the combined treatment of selenomethionine with the L-methioninase-annexin V fusion protein was lethal to human breast cancer cells, as well as tumor endothelial cells. This innovative promising therapy is currently being evaluated in breast cancer animal models.



"As a 15-year survivor and mother of two daughters, I bring a sense of urgency to my role as a consumer reviewer. By being at the table alongside scientists, I represent the voice of those who have been affected by this disease. As consumer advocates, we evaluate the innovation of the research and the likelihood that the research will benefit patients. Funding innovative research that challenges accepted paradigms is critical to making decisive reductions in mortality rates. The perspective brought by consumer reviewers helps ensure that what is funded is highly innovative and holds the promise of providing high impact to the patient community someday. Thanks to breakthroughs resulting from funding from the DOD BCRP, many more lives will be saved."

Mary Lynn Faunda Donovan
Consumer Advocate
St. Louis Breast Cancer Coalition

Heat-Sensitive Microbubbles for Intraoperative Assessment of Thermal Ablation Margins

Ronald Xiaorong Xu, The Ohio State University
FY08 Concept Award

Thermal ablation therapy uses extreme heat from sources such as radiofrequency, microwave, and laser to kill tumors by denaturing proteins and by destroying the tumor blood supply. Since the heat is applied only to the site of the tumor, thermal ablation is considered relatively noninvasive with minimal complications. However, currently this procedure is still considered highly investigative due to the lack of intraoperative techniques to measure complete destruction of cancer cells, and subsequent concerns over clinical efficacy and long-term local recurrence. Dr. Ronald Xu has developed a novel heat-sensitive agent that can potentially be used to assess intraoperative tumor ablation margins. When exposed to enough thermal energy to kill tumor cells, the biocompatible microbubbles swell significantly by merging with each other, becoming easily detectable via ultrasound and allowing optical imaging of the zone of ablation. Dr. Xu successfully used the microbubbles to image thermal ablation margins in tissue simulating phantoms, ex vivo tissues, and in vivo animal models. The next step of his research is to optimize the design of the heat-sensitive microbubbles for improved accuracy in ablation margin assessment and to incorporate targeting ligands and anti-cancer drugs for ablation-induced adjuvant therapy.

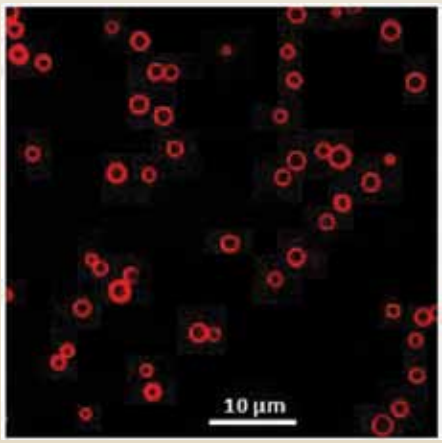


Figure 1. Confocal microscopic image of the heat-sensitive microbubbles

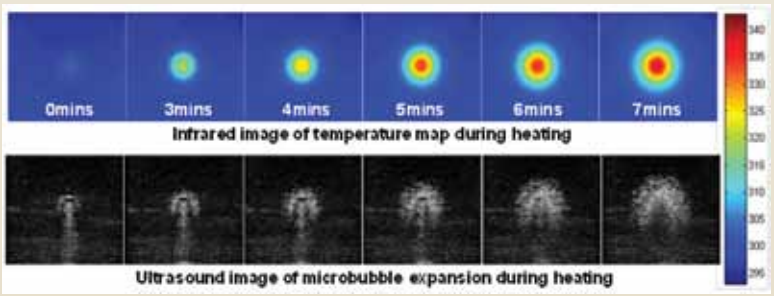


Figure 2. Ablation margin detection as heat is propagated in a tissue-simulating phantom. Adapted from the following publication with minor revision: J. Huang et. al, Biomaterials *31, 1278-1286 (2010)*

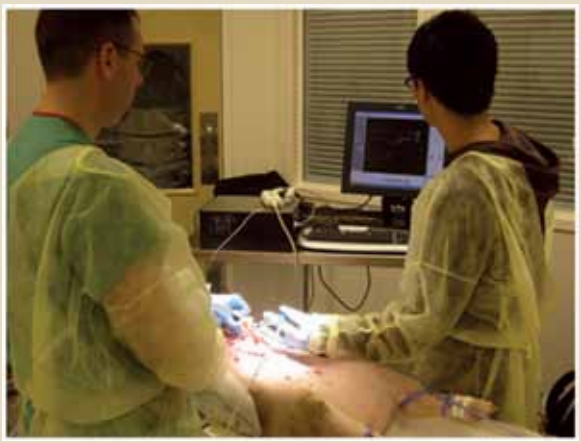


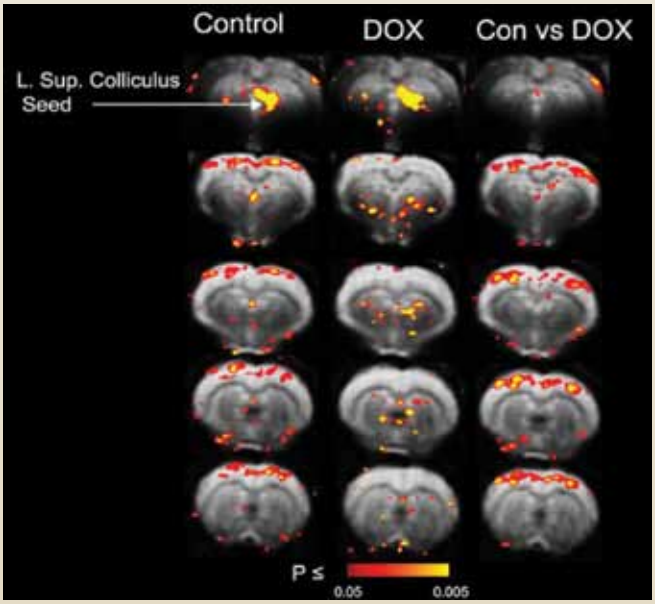
Figure 3. In vivo experiment of heat-sensitive microbubble assisted ablation margin assessment

Understanding "Chemobrain"

Alan S. Bloom, Medical College of Wisconsin
FY08 Concept Award

For decades, breast cancer patients have complained of post-chemotherapy impairment in memory and concentration that is known as "chemobrain." Understanding chemobrain at a mechanistic level requires the ability to objectively measure changes in neuronal activity in response to chemotherapy exposure. Dr. Alan Bloom has combined well-established animal behavior models with sophisticated magnetic resonance imaging (MRI) techniques to address this challenge. Female rats with and without chemically induced breast tumors were treated with weekly doxorubicin to simulate a human chemotherapy protocol, then their brains were visualized using functional magnetic resonance imaging (fMRI) as they responded to electrical stimulation of a paw, which stimulates the somato-sensory system, or a flashing light, which stimulates the visual system. In addition, fMRI was performed while the rats were in a "resting state," to look for changes in the functional architecture of the brain caused by doxorubicin.

Dr. Bloom found that doxorubicin treatment resulted in functional impairment in brain activation by sensory stimulation in regions associated with visual and somato-sensory systems. Resting state functional connectivity was decreased by doxorubicin treatment, particularly in the visual system. These effects were enhanced by pretreatment with the tumor inducer, 7,12-Dimethylbenz[a]anthracene, which in itself has no effect on brain activation. This suggests that doxorubicin action on tumors may play a role in effects on brain function, possibly due to doxorubicin's ability to trigger the formation of reactive oxygen species.



Effects of weekly DOX treatment on pMRI connectivity in the brains of female rats. A functional seed region of interest (left superior colliculus) was defined based on the group visual fMRI data. Correlation coefficients between the seed and all other voxels were then transformed to normally distributed Fisher Z values for statistical comparisons. One-sample t-tests were performed, and results are shown for the group of 9 control rats and 5 DOX rats. A two-sample t-test was performed then to determine regions where functional connectivity was greater in the control group than the DOX-treated rats. All group maps are thresholded at $p<0.05$.

The observation of functional impairment in the visual system in regard to both sensory activation and functional connectivity is of particular interest to Dr. Bloom. While direct effects on vision have not been reported, the effects of chemotherapy on visual systems function in humans have been documented by other investigators. Many of the studies that report cognitive impairment in patients also report deficits in tasks involving visual systems such as visual-spatial function or visual memory.

Making breakthroughs and new discoveries

Microenvironment Regulation of Mammary Carcinogenesis

Lisa M. Coussens, University of California, San Francisco
FY05 Era of Hope Scholar Award

Individuals suffering from chronic inflammatory diseases have an increased risk for the development of cancer in part due to the chronic presence of immune cells into malignant tissues. Although the molecular mechanisms underlying their presence in tumors are not well understood, several subsets of immune cells have been found to promote cancer development by providing the premalignant and malignant tumor cells with growth and survival factors. Dr. Lisa Coussens hypothesized that understanding the profile of breast cancer tissue infiltrating immune cells may help in predicting overall patient survival. Furthermore, she predicted that identification and validation of an immune signature might provide clinicians with a diagnostic tool that could ultimately guide breast cancer treatment decisions. Dr. Coussens investigated the immune signature profile of several immune cell subsets (CD4+, CD8+, and CD68+ cells) in breast cancer tissues encompassing ~600 patients and revealed that patients bearing a specific immune cell signature of CD68high/CD4high/CD8low had significantly reduced overall survival rates, while patients with a CD68low/CD4low/CD8high signature had longer relapse-free survival rates. Interestingly, the immune signatures were independent of breast cancer subtype, suggesting that the identified signature could be utilized to predict the overall survival rate for multiple breast cancer subtypes. The functional significance of these “immune signatures” was further evaluated in mouse models of breast cancer by depleting CD68+ immune cells with new drugs currently in clinical trials. Results from these studies demonstrated that when CD68+ cells are depleted, the presence of CD8+ cells increases in tumors and enhances the efficacy of chemotherapies used to treat recurrent breast cancer.

Elucidating the Origins of Breast Cancer Heterogeneity

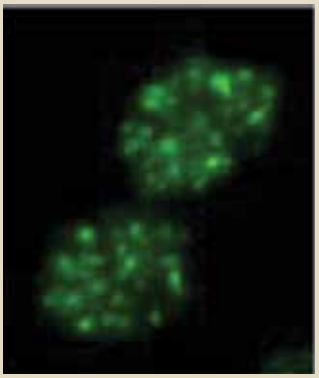
Charlotte Kuperwasser, Tufts University School of Medicine
FY07 Idea Award

Breast cancers are broadly classified as luminal-like (ER+ and/or PR+/Her2-; ER+ and/or PR+/Her2+) or basal-like (generally ER-/PR-/Her2-) tumors based on their receptor profiles. The rarer basal-like tumors tend to be aggressive and more limited in treatment options. Although these receptor profiles have been utilized to predict patient outcomes, the mechanism(s) responsible for the development of the breast cancer subtypes is not well understood. Furthermore, it is unclear whether luminal-type tumors are derived from luminal cells and whether basal-like tumors are derived from basal cells. Dr. Charlotte Kuperwasser hypothesized that a better understanding of the influence of luminal and basal cells on the development of the various breast cancer subtypes would contribute to establishing more effective treatment strategies and novel diagnostic biomarkers. In support of the hypothesis, she utilized a humanized mouse model to investigate the ability of luminal cells and basal cells to develop into the different breast cancer tumor subtypes. In mice, luminal cells developed into expansive tumors while basal cells formed small palpable tumors, which contained features similar to human basal-like tumors. Interestingly, the luminal cells formed both luminal- and basal-like tumors, demonstrating for the first time that the majority of human breast cancers are likely derived from cells within the luminal breast lineage.

The Bridge Between BRCA1 and BRCA2 in Breast Tumor Suppression

Xiaochun Yu, University of Michigan
FY09 Era of Hope Scholar Award

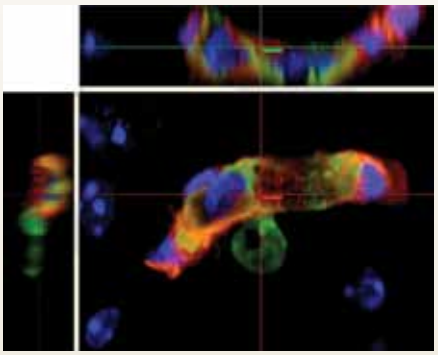
Deleterious mutations in the BRCA1 and BRCA2 tumor suppressor genes predispose individuals to hereditary breast, ovarian, and other cancers. Both BRCA1 and 2 are implicated in repairing routine DNA damage that cells accumulate from various environmental stresses. When deleterious mutations are present on either of these genes, DNA repair is compromised, resulting in genomic instability and an increased risk of developing cancer. While the individual roles of BRCA1 and 2 in DNA repair are well established, it is unclear whether the two genes function together in the same DNA damage response pathway. In preliminary studies, Dr. Xiaochun Yu established PALB2 as the functional link between BRCA1 and BRCA2, demonstrating for the first time that PALB2 may be another breast tumor suppressor gene and that BRCA1 is an upstream regulator of BRCA2 in the DNA damage response. Dr. Yu is further examining the molecular mechanisms of DNA repair, its role in breast tumorigenesis, and possible therapeutic approaches to repair the mutated tumor suppressors in compromised cells.



PALB2 at DNA damage sites in human breast cancer cells.

Understanding and Fighting Breast Cancer Brain Metastasis

Brunhilde Felding-Habermann, Scripps Research Institute
FY07 Idea Award



Breast cancer cell penetrating the blood brain barrier. Human breast cancer cells shown inside and emerging from brain capillary in a mouse model. Green: human breast cancer cells, Red: endothelial marker of blood vessel, Blue: nuclei
Photographer: Mihaela Lorger; Owner: M. Lorger and Brunhilde Felding-Habermann; Courtesy of the American Journal of Pathology*; (This image had been published in the* American Journal of Pathology*, Vol. 176, No 6, June 2010)*

The brain is one of the most common sites for breast cancer metastasis, affecting up to 20%–35% of patients with advanced breast cancer. The most commonly used treatment options are surgery and whole-brain radiation, which unfortunately are not curative. Patients presenting with brain metastases have only a 2%–5% 5-year survival rate, in part due to the therapeutic blockade imposed by the blood-brain barrier.

Neural progenitor cells have the innate ability to actively seek out and infiltrate brain metastases after intrabrain transplantation. To develop novel therapeutic strategies for treating brain metastases, Dr. Brunhilde Felding-Habermann hypothesizes that neural progenitor cells may be genetically modified to secrete therapeutic molecules directly into the tumor. In support of this hypothesis, Dr. Felding-Habermann and colleagues established new breast cancer metastasis models from patient samples to emulate all steps of human breast cancer brain metastasis development and invasive progression. The researchers focused on establishing the initial events that lead to brain metastasis by identifying and characterizing cell subpopulations that have distinct intracranial growth properties and may be functional therapeutic targets. Surprisingly, preliminary results contradict the current dogma of metastatic initiation: the researchers found that brain metastatic breast cancer cells with putative stem cell biomarkers do not exhibit aggressive brain metastatic growth. The researchers are currently assessing the molecular profiles of cell subpopulations that do exhibit aggressive growth to identify new potential targets for therapeutic intervention for breast cancer brain metastases.

Maternal Consumption of Omega-3 Fatty Acids May Prevent Breast Cancer in Offspring

W. Elaine Hardman and Philippe Georgel, Marshall University
FY09 Idea Expansion Award

The omega-3 fatty acid is an essential nutrient commonly found in some plants and fatty fish. Results from animal studies indicate that omega-3 fatty acid consumption can inhibit breast cancer growth, and epidemiological studies indicate that people who consume higher amounts of omega-3 have a reduced risk of developing cancer. Based on these observations, Drs. Elaine Hardman and Philippe Georgel of Marshall University hypothesize that maternal consumption of omega-3 during pregnancy could reduce the risk of breast cancer in the offspring by inducing permanent epigenetic changes in the offspring DNA. The investigators aim to determine specific gene expression changes induced by omega-3 consumption in the offspring by feeding pregnant mice a diet containing canola oil (a source of omega-3) or a diet containing corn oil (control). Initial data analysis comparing the two groups indicates differences in expression profiles of genes related to mammary tumorigenesis, such as NF-kappaB, as well as differences in epigenetic and microRNA expression profiles. The preventive potential of omega-3 will be assessed by comparing mammary cancer incidences of the offspring groups after exposure to a carcinogen.

Understanding risk and disparity

Next Generation Education for Prevention: Defining Attitudes, Concerns, Educational Needs, and Life Plans of 18- to 24-Year-Old Daughters of BRCA1/2 Mutation Carriers

Andrea Patenaude, Dana-Farber Cancer Institute
FY08 Idea Award

Women carrying BRCA1/2 mutations have a 56%–85% risk of developing breast cancer in their lifetime. Unfortunately, the daughters of BRCA1/2 mutation carriers have a 50% chance of inheriting this high breast cancer risk. Genetic testing of at-risk women is not recommended below age 18. Targeted screening for young at-risk women is recommended to begin at age 25. Knowledge of hereditary risk has the potential to enable initiation of breast cancer screening at age 25 that can lead to breast cancer detection at an earlier, treatable stage and may play a significant role in reducing the morbidity and mortality associated with hereditary breast cancer. Dr. Andrea Farkas Patenaude hypothesized that this high-risk group of women age 18 to 24 years do not fully comprehend their breast cancer risk and the options for risk reduction or prevention, and, therefore, they delay genetic counseling and testing and often do not begin appropriate screening at age 25. In light of this, Dr. Patenaude has initiated a study to evaluate the genetic knowledge, decision making, distress, life plans, and health behaviors of daughters of BRCA1/2 mutation carriers, to develop a psycho-educational intervention that will promote early genetic screening and counseling for this high-risk group. Preliminary data suggest that this group of high-risk young women is generally inadequately informed about breast cancer genetics and risk reduction options and that they have high levels of distress related to worry about hereditary cancer for themselves and their family members. These data highlight the need for educational interventions targeting this high-risk group.

"I was excited to participate in the BCRP because of the innovative research that is made possible by this funding source. As a huge supporter of research, my role as a consumer reviewer provides me with an opportunity to sit at the table with scientists and provide input that matters. Additionally, I feel it is my responsibility to provide a voice and face of the target population in this process. Due to this program's mission, I am encouraged that there will be an eradication of breast cancer in my lifetime."

Wanda Lucas
Consumer Advocate
Young Survival Coalition

Spatially Informed Investigations of Race-Specific Social Gradients in Breast Cancer Disparities

Ann Klassen, Johns Hopkins University
FY06 Synergistic Idea Award

Although the total incidence of breast cancer is higher in Caucasian women, breast cancer in African American women tends to occur at a younger age, is more aggressive and diagnosed at more advanced stages, and is less responsive to treatment. Due to these ethnic disparities, a better understanding of the influence of social conditions on breast cancer burden is needed to aid public health efforts to decrease the prevalence and burden of this disease. Dr. Ann Klassen, in partnership with Dr. Frank Curriero of Johns Hopkins University, is investigating the influence of social class and material resources on ethnic disparities associated with breast cancer. Her research team is analyzing social class data, such as education level, employment status, and income, as well as material resources data, such as households with cars and telephones, poverty, and home ownership to predict breast cancer burden. Her team has correlated social class and material resources with breast cancer tumor size, histological grade and type, and stage of disease at diagnosis. Interestingly social class was a strong predictor for breast cancer tumor grade, size, and type in Caucasian women, while material resources were a stronger predictor for breast cancer tumor grade and size in African American women. Social class was also determined to be a strong predictor for breast cancer stage at diagnosis for African American women. Women of both races living in areas with higher social class or material resources were less likely to have late-stage diagnoses. Based on these observations, Dr. Klassen concluded that there are social differences that may account for the racial disparities in breast cancer burden. These important research findings offer not only a better understanding of breast cancer disparities but may influence future public health efforts.

Image-Based Biomarkers to Analyze Breast Cancer Disparity Among African-American Women

Fengshan Liu, Delaware State University
FY08 HBCU/MI Partnership Training Award

Ethnic and racial differences (e.g., genetic predisposition and breast density) can influence breast cancer risk, subtype, treatment, and prognosis. Dr. Fengshan Liu is establishing an interdisciplinary breast cancer research program at Delaware State University in partnership with University of Pennsylvania. Through the HBCU/MI Partnership Training Award, faculty members at Historically Black Colleges and Universities or Minority Institutions receive mentored training toward becoming independent breast cancer investigators and establishing a breast cancer research program at their institutions. Dr. Liu and colleagues are identifying imaging-based risk biomarkers in minority women to develop personalized approaches for breast cancer surveillance and prevention. With the goal of establishing a method to accurately identify minority women at an increased risk of developing breast cancer, the investigators are currently assessing racial differences in breast physiology by analyzing clinical breast images of approximately 11,100 cancer-free women. The results will be applied to create a breast cancer risk prediction model for African American women.

The BCRP Multi-Team Award supports the creation of a collaborative, innovative research project among three teams composed of scientists, clinicians, and consumer advocates to focus on a critical area of breast cancer. The multi-team approach is expected to transform the research process through the integration of basic and clinical disciplines, cross-disciplinary training, and consumer advocate participation.

Breast Cancer: Catch It with Ultrasound

Lianjie Huang,[1] Donald Ingber,[2] and Michael Williamson[3]

[1]Los Alamos National Laboratory, [2]Children's Hospital, Boston, and [3]University of New Mexico

Consumer Advocates: Erin Bouquin, Peggy Devine, Nancy Hawkins, and Elizabeth Harris

FY09 Multi-Team Award

Drs. Huang, Ingber, and Williamson are teaming together to develop a novel, safe, and cost-effective breast imaging technique that will vastly improve breast cancer detection and diagnostic imaging. This next-generation ultrasound tomography (UST) technology aims to significantly increase sensitivity and specificity of breast cancer imaging by integrating recent advances in three-dimensional geophysical tomography with the biomechanical features and structural properties of normal and cancerous breast tissues at different stages of cancer progression. Three-dimensional UST holds great promise for overcoming some of the major limitations of current imaging techniques such as low resolution, artifacts, radiation exposure, and interference from dense tissue. In addition to direct clinical relevance in imaging breast cancer, this new UST technology also will provide a way to study the biomechanics of breast cancer progression in vivo and may lead to the identification of new therapeutic approaches to the treatment of breast cancer.

Building a Better Model: A Comprehensive Breast Cancer Risk Model Incorporating Breast Density to Stratify Risk and Apply Resources

Jennifer Harvey,[1] William Knaus,[1] and Martin Yaffe[2]

[1]University of Virginia and [2]Sunnybrook Health Sciences Centre

Consumer Advocates: Carolyn Achenbach, Sylvia Tyree, Vernal Branch, and Kathleen Gallagher-Ross

FY10 Multi-Team Award

The debate surrounding the question of when women should begin and how frequently they should have mammograms has intensified in recent years. While there is clearly a benefit in detecting invasive breast cancers early, it is countered by the harms resulting from false positives and over-diagnosis. Drs. Harvey, Knause, and Yaffe have teamed up in an effort that will provide more individualized information on breast cancer risk to help women make better decisions regarding screening. They will develop a risk/benefit ratio model that incorporates data on heritable and personal risk factors (such as family history, BMI, alcohol use, exercise, age) combined with computerized measurements of breast density. Breast density is a strong risk factor for development of breast cancer, yet it is not incorporated into the current risk models. The first step will involve establishing the best method for automated computerized measurement of breast density. Next, they will develop and test their new model in local populations before following up with a national-level study for further validation. The results of this study will move beyond population-based guidance to provide personalized information regarding breast screening for women.

Enhancing the Breadth and Efficacy of Therapeutic Vaccines for Breast Cancer

Peter P. Lee,[1] Paul Spellman,[2] and Jill Slansky[3]

[1]City of Hope Beckman Research Institute, [2]Oregon Health & Science University, and [3]University of Colorado at Denver

Consumer Advocates: Susie Brain, Joan Venticinque, and Carolyn Charkey

FY10 Multi-Team Award

A significantly better outcome has been observed in patients when immune system T cells are found in their breast cancer tissue or in local lymph nodes. Drs. Lee, Spellman, and Slansky are bringing together teams with expertise in genomics and immunology in a focused effort to enhance the T cell anti-tumor response and improve the immune system's ability to fight breast cancer. Together, they will identify and validate specific breast cancer antigens that are recognized by T cells and further characterize those antigens according to specific subtype (luminal, basal, HER2) and/or whether they are present on breast cancer stem cells. To augment the T cell-mediated killing of tumor cells, the group will also identify small molecule agents that promote tumor cell apoptosis. Overall, the information generated by these studies will contribute directly to the development of improved personalized immunotherapies for breast cancer.

Radiation-Induced Vaccination to Breast Cancer

Silvia Formenti,[1] Sandra Demaria,[1] and William McBride[2]

[1]New York University School of Medicine and [2]University of California, Los Angeles

Consumer Advocates: Ginny Mason, Alice Yaker, Flona Todd, BJ Dockweiler, and Amy Bonoff

FY10 Multi-Team Award

Almost a third of all patients diagnosed with invasive breast cancer will eventually succumb to metastatic disease. Drs. Formenti, Demaria, and McBride have joined their teams together to test the novel hypothesis that a tumor-specific protective immunity can be induced in breast cancer patients by irradiating a local metastatic site in the presence of transforming growth factor beta (TGF beta) blockade. The neutralizing antibody Fresolimumab will be used to block TGF beta and activate the immune system, while the local radiotherapy will generate a burst of immunogenic and tumor-specific antigens. This combinatorial approach is designed to engage the patient's own immune system in providing systemic control of tumor growth beyond just the targeted metastatic site. If successful, this would create a new therapeutic strategy of individualized vaccination and enable long-term management of metastatic disease.

The BCRP Transformative Vision Award supports research projects to realize an extraordinary vision for dramatically affecting the prevention or treatment of breast cancer and a plan to test and achieve the vision as quickly as possible through the translation of these ideas into patients.

Vaccine to Prevent Breast Cancer

Mary Disis

University of Washington

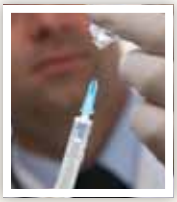
FY10 Transformative Vision Award

Vaccines have proven to be extremely successful in preventing diseases caused by common pathogens. The vision of Dr. Disis and her group is that breast cancer initiation could be prevented by immunizing individuals against upregulated proteins that are associated with breast cancer stem cells and epithelial to mesenchymal transition (EMT). To achieve this vision, she is first identifying new stem cell/EMT antigens and screening them for epitopes that have the ability to preferentially elicit a T helper 1 (Th1) immunity instead of the more typical immunosuppressive Th2 response. Based on these results, a multi-antigen/polyepitope vaccine will be constructed and tested for safety and immunogenicity in mouse models. The first human test of the stem cell/EMT vaccine would be on triple-negative breast cancer patients who are in remission, with the goal of preventing recurrence. If it is determined to be safe and effective, this vaccine strategy could then be employed to prevent the development of breast cancer in women who are at high risk.

Achievements at a Glance:

Intraductal Techniques
Susan Love
FY93 Idea Award
FY95 Investigator-Initiated Award

Most breast tumors appear to arise in the cells lining the milk ducts of the breast. With BCRP support, Dr. Love looked for early evidence of cancer in the ducts by modifying an endoscope to enter and examine milk ducts through their openings at the nipple. Her research increased understanding of duct architecture, most importantly in providing strong evidence that early-stage breast cancer is confined to a single duct system. She laid the groundwork for the development of increasingly sophisticated and miniaturized endoscopes that allow the retrieval of cell samples for analysis, the precise location of intraductal lesions for excision, and the potential to deliver breast cancer therapy intraductally.



E75 Her2-Derived Peptide Vaccine (NeuVax™)
Constantine Ioannides
FY96 Idea Award

BCRP supported Dr. Ioannides' study that sought to identify cytotoxic lymphocyte-recognized epitopes on Her2-overexpressing human breast tumors, during which E75 (an immunodominant HER2 peptide) was discovered together with Dr. Bryan Fisk. The E75 peptide has since been developed by Dr. George Peoples into an immunogenic peptide-based vaccine under the commercial name of NeuVax (Galena Biopharma). NeuVax will enter Phase III clinical trials in 2012.

HER2 Bi-Armed Activated T Cells
Lawrence G. Lum
FY99 Concept Award

BCRP supported the preclinical studies on armed activated T cells, which induces the development of "memory" antigen-specific cytotoxic T lymphocytes directed at Her2. This led to a Phase I clinical trial in women with Her2+ metastatic breast cancer, which indicated that the treatment infusions are safe and induced long-term anti-tumor responses. The Her2 Bi-armed activated T cells are currently in Phase II clinical trials for treating women with stage II or III breast cancer and women with metastatic breast cancer.

"Without the funding that was initiated by the original Concept Award, the development of the Her2 Bi product might not have happened. Thank you very much for a great opportunity!"

ErbB2/ErbB3 Bispecific ScFv (ALM) Antibody
Gregory Adams
FY99 Concept Award

BCRP supported preclinical studies to develop and test an engineered bispecific single chain Fv antibody capable of simultaneously engaging both HER2 and HER3. This novel agent was designed to enhance therapeutic effects on breast cancers that express both HER2 and HER3 and block the potent pro-growth signaling that occurs when these tumor-associated antigens engage each other upon ligand binding. Resulting technology and parent antibodies were licensed by Merrimack Pharmaceuticals, which developed the agents and concepts into a drug called MM-111, which is currently in early phase clinical trials for treating patients with Her2+ advanced breast cancer.

In the Pipeline

Prone Radiotherapy
Silvia Formenti
FY00 Idea Award

With BCRP support, Dr. Formenti conducted clinical trials to assess the efficacy of accelerated, hypofractionated partial or whole-breast radiation therapy designed to minimize the length of radiotherapy required after partial mastectomy in selected patients with invasive breast cancer and DCIS. In this method, patients are treated in the prone (i.e., while lying on the stomach) position rather than in the supine (i.e., while lying on the back) position on a specially designed table, greatly reducing unnecessary radiation exposure of the heart and lungs. Importantly, prone radiotherapy offered heart and lung protection regardless of breast size. Prone radiotherapy is poised to become a standard choice in breast radiotherapy, with industry already adopting modifications of standard radiotherapy tables to better enable this approach.

IDO Inhibitor
George C. Prendergast
FY02 Idea Award

Indoleamine 2,3-Dioxygenase (IDO) is an enzyme that is commonly activated in breast cancer and is implicated in preventing the anti-tumor immune response by blocking T cell activation. BCRP supported the preclinical studies that identified and characterized lead inhibitors of IDO that have pharmacological properties suitable for testing in clinical trials. As a result of this work, Dr. Prendergast demonstrated that the D isomer of an IDO inhibitor called 1MT (D-1MT) has superior anti-tumor properties, and his group discovered IDO2, an IDO-related gene, as one of its important molecular targets. D-1MT is now entering Phase II clinical trials for breast cancer and other cancers, alone or in combination with other drugs, having shown some provocative responses in Phase I/IB trials now completed.

"The unusually rapid translation of IDO inhibitors from an obscure stage of preclinical study to Phase I clinical trials seeded by this DoD project represents a notable success for the DoD Breast Cancer Research Program."

Optical Spectroscopy
Nimmi Ramanujam
FY04 Era of Hope Scholar Award

With BCRP support, Dr. Ramanujam is developing novel optical tools and optically detectable biomarkers that report on the physiological, metabolic, molecular, and morphological state of breast cancer in real-time. These tools will have the flexibility to be implemented during surgery (lumpectomies) or at the time of image-guided percutaneous biopsy. By accurately assessing tumor margins during lumpectomies and providing molecular information during biopsies, the tools will potentially eliminate the need for repeated surgeries, and assist the clinician in making treatment decisions.

"My research wouldn't be possible without funding and support from the Breast Cancer Research Program and their belief in our technology."

Molecular Breast Imaging
Carrie Hruska
FY06 Multi-Disciplinary Postdoctoral Award

Molecular breast imaging (MBI) is a nuclear medicine technique that uses high-resolution dual-head gamma cameras to detect the functional uptake of a radiotracer in the breast. Following a Mayo Clinic study that demonstrated MBI to be more sensitive than conventional mammograms for detecting breast cancer in women with dense breasts, BCRP funded work to evaluate the concordance of MBI with magnetic resonance imaging of the breast, to investigate the effects of fluctuating hormonal levels on the appearance of MBI, and to develop important quantitative analysis software for MBI. Later clinical trials demonstrated that MBI may be used to monitor patients' response to chemotherapy. Currently, two FDA-approved MBI units are commercially available.

Achievements at a Glance:

BRCA2 617delT Mutation
David Goldgar and Susan Neuhausen
FY93 Investigator-Initiated Award

Breast cancer and ovarian cancer risk is greater in individuals with mutations in the BRCA1 and BRCA2 tumor suppressor genes. The likelihood of BRCA1 or BRCA2 mutations is higher in certain populations, including individuals of Ashkenazi Jewish descent. BCRP funding contributed to the discovery of the BRCA2 617delT mutation, one of the three founder BRCA1/2 mutations that occur in Ashkenazi Jews. The BRCA2 617delT mutation is now part of a commercialized test for BRCA1/BRCA2 gene mutations in this risk group.

Carolina Mammography Registry
Bonnie Yankaskas
FY93 Information Systems Award

The Carolina Mammography Registry was first funded by a BCRP award to create the infrastructure for a population-based mammography registry in North Carolina, focusing on a largely rural population. In 2005, the registry became a member site of the NCI Breast Cancer Surveillance Consortium, a national registry that includes data from mammography registries in North Carolina, New Hampshire, Vermont, New Mexico, California, and Washington. This database provides a resource for researchers to study mammography screening on a national level.

Herceptin®
Dennis Slamon
FY93 Investigator-Initiated Award

Herceptin (trastuzumab) is a monoclonal antibody that targets the human epidermal growth factor receptor 2 (HER2) receptor. HER2+ breast cancer accounts for approximately 25% of all breast cancers. The BCRP was instrumental in supporting the preliminary in vitro and in vivo studies needed to test the efficacy of Herceptin, which later led to clinical trials and commercialization. Herceptin revolutionized breast cancer treatment and the field of targeted therapeutics. Herceptin is now part of standard-of-care treatment regimens for HER2+ early-stage and metastatic breast cancers.

Margaret Dyson Family Risk Assessment Program
Mary Daly
FY93 Tumor Sample, Breast Tissue, and Cell Line Repositories Award

The BCRP supported the establishment of a high-risk breast cancer registry to gather genetic and environmental risk information about women with familial breast cancer. This registry evolved into the Margaret Dyson Family Risk Assessment Program for individuals at risk for breast or ovarian cancers. This program, which serves Philadelphia and its surrounding communities, now provides a range of risk assessment, screening, and preventive services to individuals who have a family history of breast or ovarian cancer.

PTEN Tumor Suppressor Gene
Michael Wigler
FY93 Investigator-Initiated Award

BCRP funding contributed to the original discovery of the PTEN (phosphatase and tensin homolog) gene. In normal cells, PTEN functions as a tumor suppressor protein that helps regulate cell division and growth. PTEN is one of the most frequently mutated genes in several cancers, and PTEN mutations have been shown to be predictive of aggressive cancer. PTEN mutations also occur in a group of genetic syndromes that are characterized by malignant and benign tumors. A PTEN test is commercially available to confirm PTEN mutations for clinical and prenatal diagnoses and identification of at-risk family members.

ATLAS Clinical Trial
Richard Peto
FY93 Investigator-Initiated Award

BCRP funds supported initiation of the Phase III clinical trial ATLAS (Adjuvant Tamoxifen Longer Against Shorter), the largest breast cancer treatment trial ever undertaken. Adjuvant tamoxifen is the first-line treatment for early-stage estrogen receptor -positive(ER+) breast cancer. The focus of the ATLAS trial was to examine whether 10 years of adjuvant tamoxifen confers greater benefit overall than 5 years of adjuvant tamoxifen. The clinical trial was initiated in 1996 and completed randomized accrual in 2005. Women with early-stage ER+ breast cancer who had completed 5 years of adjuvant tamoxifen were randomized to either continue for another 5 years or to stop the treatment. Preliminary analysis indicated that recurrence rate was significantly lower among those who continued tamoxifen treatment. ATLAS is currently in the follow-up phase until 2015.

Making an Impact

Sentinel Lymph Node Biopsy
Kathryn Verbanac
FY97 Career Development Award

The previous standard for detecting breast cancer invasion into the lymph nodes was to remove the majority of axillary lymph nodes and search for cancer cells. In a significant proportion of women, this causes lymphedema, a condition that compromises functionality and quality of life. In sentinel lymph node biopsy, lymph node removal is limited to only the first few nodes that receive lymph drainage from the breast. This diagnostic/prognostic technique enables clinicians to determine tumor staging and if more extensive lymph node surgery is necessary. The BCRP provided funding for a multicenter clinical trial I to validate sentinel lymph node biopsy as an accurate method to predict the presence of disease in the axillary lymph nodes.

Skp2 Oncogene
Michele Pagano
FY99 Concept Award

The BCRP supported the establishment of Skp2 as an oncogene that is overexpressed in human breast tumors. High Skp2 expression correlating with destabilization of p27 was found to be associated with poor prognosis in breast cancer patients. These findings contributed to the practice of Skp2/p27 immunohistochemical analysis as a prognostic test performed in clinical pathology laboratories.

OncoVue®
Eldon Jupe
FY00 Idea Award

Risk-association studies funded by the BCRP formed the foundation for a breast cancer risk assessment test that is now commercially available. Single nucleotide polymorphisms (SNPs) are DNA sequence variations that occur when a single nucleotide (A, T, C, or G) in the genome sequence is altered. OncoVue is the first genetic-based breast cancer risk test that incorporates a woman's SNPs with personal history to estimate her risk for breast cancer. This test can identify high-risk patients and enable clinicians to individualize breast cancer screening and monitoring. OncoVue is commercially available and is currently offered at over 30 breast care centers in the United States.

Three-Dimensional Cell Culture Systems
Mina Bissell
FY01 Innovator Award

The BCRP supported the development of 3D culture systems that have made important contributions in understanding the tissue microenvironment and how interactions between epithelial cells and the extracellular matrix control cancer development. As surrogates for in vivo studies, 3D culture models have enabled the elucidation of oncogenic and other cell signaling pathways that are controlled by cell-matrix interactions. 3D culture models are currently utilized across academic laboratories and by drug companies as screening assays to test for therapeutic response.

BreastCancerTrials.org
Laura Esserman
FY02 Breast Cancer Center of Excellence Award

Breast cancer patients can benefit from objective information about clinical trials. The process of identifying an appropriate clinical trial by performing independent research is challenging. The BCRP funded a Breast Cancer Center of Excellence Award that contributed to the development of a website (BreastCancerTrials.org) that educates patients about breast cancer clinical trials and matches them with appropriate trials.

Expression Arrest™ shRNA Libraries
Gregory Hannon and Stephen Elledge
FY01 and FY03 Innovator Awards

RNA interference (RNAi) is a cellular system that controls which genes are active or silent. The selective effect of RNAi on specific gene expression makes it a valuable research tool. Small hairpin RNAs (shRNAs) are one of the gene silencing mechanisms of RNAi. The BCRP supported the development of whole genome shRNA libraries that target over 30,000 genes. This commercially available research tool provides researchers with ready-to-use, rapid RNAi screens for the entire human and mouse genomes to study gene regulation and identify new therapeutic targets in many diseases and conditions, including cancer.

For more information, visit
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