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 nearly $7 billion in appropriations from its inception through fiscal year 2012 (FY12). 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, which is composed of leading scientists, clinicians, and consumer advocates. The Integration Panel compares applications to each other and makes recommendations for funding based on scientific merit, portfolio balance, 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 nearly $2.8 billion in appropriations to the program, including $120 million in FY12. 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 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 future generations of breast cancer experts. Recognizing the need to promote team science, the BCRP also created unique award mechanisms that foster synergistic, meaningful research partnerships. Through its award mechanisms and innovative approach, the BCRP plays a leading role in the breast cancer research community.

The BCRP enables the scientific community to propose the most innovative and high-impact ideas that address the urgent need to end breast cancer.

VISION

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

FY92–FY11 BCRP Portfolio

- Cell Biology: 27%
- Endocrinology: 6%
- Genetics and Molecular Biology: 12%
- Immunology: 2.5%
- Primary Prevention: 1.5%
- Pathobiology: 12.8%
- Complementary and Alternative Medicine: 0.5%
- Detection and Diagnosis: 10.3%
- Clinical and Experimental Therapeutics: 17.4%
- Biobehavioral Sciences: 1.8%
- Epidemiology: 3.4%
- Health Care Delivery: 0.8%
- Research Resources: 3.3%
- Breast Cancer Research Program: 3
Strategic Partnerships:

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 breast cancer survivors (consumers). This innovative approach, which has since been adopted by other funding organizations, is a highly proven and effective way to evaluate research applications for their potential to make a meaningful impact and contribute to the program’s vision of ending breast cancer.

Did you know...

* Consumer advocates participate in designing the BCRP’s priorities and funding opportunities?
* Consumer advocates participate as equal voting members in making funding recommendations during programmatic review?
* Consumer advocates participate as equal voting members in scientific peer review panels?
* More than 3,500 scientists and 730 consumers have contributed their expertise to the BCRP two-tier review process?

“The urgency for progress is a powerful force in the BCRP, generating new ideas for translating basic research into solutions for breast cancer in this unique collaboration between scientists and consumer advocates.”

Frank Calzone  
FY13 Integration Panel Chair

“The BCRP’s work is important in sparking innovation in research aimed at ending breast cancer. Consumers work together with laboratory and clinical scientists on the Integration Panel and it is one of the important ways in which I choose to express my breast cancer advocacy. The BCRP’s focus on innovation and impact of breast cancer research is a crucial aspect of eradicating this terrible disease and doing so as soon as possible.”

Ngina Lythcott  
Black Women’s Health Imperative  
FY13 Integration Panel Member

Breast Cancer Research Program
The BCAP has enabled partnerships through team-oriented award mechanisms, in which scientists and consumers work together to establish research project goals and collaborate on the design and implementation of innovative research.
Investing in the next generation of innovators

Development of a Novel Intraoperative Optical Imaging Device of Breast Cancer
Yang Liu, Washington University
FY10 Predoctoral Traineeship Award

One of the challenges facing current breast cancer management is the lack of accurate, real-time, functional imaging devices for the surgical resection of tumors and lymph node biopsy, a standard breast cancer staging procedure. Under the mentorship of Dr. Samuel Achilefu, Mr. Yang Liu is developing a miniaturized intraoperative imaging device that is designed to be simple, accurate, and affordable. Such a device could provide real-time guidance to aid surgeons in identifying and excising breast tumors and positive lymph nodes. Mr. Liu also proposed to equip the device with real-time communication capabilities to facilitate collaborations between clinicians at large medical institutions and their counterparts in rural hospitals.

With the concept of wearable imaging systems, Mr. Liu has developed a fluorescence goggle that is compact, lightweight, and operates using AA batteries, enabling the system to be very portable. The fluorescence goggle is very sensitive in detecting molecular probes and allows surgeons to operate the device in a hands-free manner. In animal studies, the prototype goggles have been used both to image sentinel lymph nodes dyed with trace dosages of molecular probes and to excise nonobvious small tumor nodules in mice. Mr. Liu's work in developing an improved surgical imaging platform could aid surgeons in ensuring complete tumor resection, thereby improving prognosis for patients with breast cancer.

“The is never any doubt that my perspective as a breast cancer survivor is greatly valued by the BCRP. My experience working with prominent scientists and other breast cancer advocates in helping determine how the money appropriated by Congress will be invested in research has translated into inspiration and hope.”

Margerie Manning
Consumer Reviewer
San Luis Young Survivors
Kinases as Targets for Breast Cancer Therapy
Yashaswi Shrestha, Dana-Farber Cancer Institute, Boston
FY08 Predoctoral Traineeship Award

Kinases are key regulators of cellular function. Several kinases have been shown to be activated or mutated in breast cancer. A rapidly emerging area of drug discovery includes the development of small molecular inhibitors of kinases implicated in cancer and other diseases. Under the mentorship of Dr. William C. Hahn, Dr. Yashaswi Shrestha investigated and identified novel kinases as potential targets for breast cancer therapy.

Using a publicly available dataset of more than 3,000 human tumor samples and cancer cell lines, Dr. Shrestha found that the kinase PAK1 is amplified in several cancers, but most commonly in breast cancer. In breast cancer cell lines with PAK1 amplification, Dr. Shrestha observed that PAK1 is necessary for anchorage-independent growth, an indicator of cellular transformation to a cancer phenotype. She also observed that another kinase, PTK6, was shown to be amplified in more than 50% of the breast tumor samples contained in the dataset. In human mammary epithelial cell (HMEC) lines, PTK6 was not able to induce anchorage-independent growth by itself but cooperated with other kinases to enhance anchorage-independent growth. Furthermore, Dr. Shrestha showed that the mechanism by which both PAK1 and PTK6 mediate cellular transformation was through activation of the RAS/MAPK signaling pathway, which, when overactivated, can lead to uncontrolled cellular growth. Dr. Shrestha's work, performed during the course of her doctoral research, has revealed two novel kinases that are amplified in human breast cancer and may serve as candidate targets for breast cancer therapy.

Novel Drug Discovery Through a Mentored Collaboration
Mandip Sachdeva, Florida A&M University
FY10 Inter-Institutional Training Award

Novel treatment options for breast cancer are urgently needed to overcome the problems of disease recurrence and resistance to current therapies. Dr. Mandip Sachdeva at Florida A&M University (FAMU), recipient of an Inter-Institutional Training Award, has established a mentored collaboration with Dr. Stephen Safe of Texas A&M University to expand upon Dr. Safe’s discovery of a new class of drug analogue. Dr. Safe previously found that analogues of diindolylmethane (DIM), a phytochemical product found in cruciferous vegetables, demonstrated significant anticancer activity. Dr. Sachdeva and his FAMU co-investigators, Dr. Barack Abonyo and Dr. Musiliyu Musa, are working with Dr. Safe to develop novel C-DIM (C-substituted DIM) analogues that inhibit cancer growth and may have major clinical implications for breast cancer. The Inter-Institutional Training Award mechanism provides focused mentoring and training for new faculty-level breast cancer researchers and a foundation for establishing a breast cancer research program at the primary institution. By training with Dr. Safe in drug development technology, the investigators are strengthening FAMU’s research capabilities in breast cancer. Moreover, this joint project lays the groundwork for advanced preclinical testing of these novel drugs for treatment and chemoprevention.
It has been shown that breast cancer is not just one disease but a complex array of diseases that can be divided into subtypes that should be treated with specially targeted therapeutics. Researchers are now beginning to reveal compelling data about the molecular signatures of these subtypes that indicate that, even within a subtype, treatment may be made more efficacious by adjusting therapy for the individual patient. During his doctoral training, Dr. Adam de la Zerda developed new imaging tools that are capable of providing important information about the response of the disease to therapy soon after its initiation, thus offering clinicians the opportunity to quickly devise alternative therapies if tumor response to treatment is poor. Dr. de la Zerda talks about his research and his experience as a BCRP-funded predoctoral candidate:

**How did you formulate your research question?**

Through interactions with other lab members and breast cancer surgeons during my graduate studies, I became aware there was a clinical need for technology to measure disease response. At that time I was an electrical engineer who worked in a biological lab, and so I brought electrical engineering tools to solve this need. In fact, I was using the photoacoustic effect (initially discovered by Alexander Graham Bell in 1880) where light is converted into sound by certain molecules. I built a system that shines light on a tissue and measures the sound waves that emerge out of the tissue in response. By measuring the sound waves from multiple angles, I was able to create a three-dimensional (3-D) map of the tissue and show the molecular activity of the tumor.

**What is the next step to bringing your research closer to helping patients with breast cancer?**

I have shown that this research is effective in animal models. The next step is to test this approach in patients. The funding I received from the BCRP has allowed me to build the very first photoacoustic molecular imaging system. Once my initial work was completed, my graduate advisor, Professor Sam Gambhir, and I successfully competed for a number of grants (e.g., NCI U54 Center Grant) that will enable the translation of this technology into the clinic.

**What is important to you about this work?**

I am not trying to find a drug that will help alleviate symptoms of advanced-stage breast cancer. Rather, my research aims to make personalized medicine of breast cancer a reality by providing early indication of treatment efficacy so that the 70% of patients who will not respond to the drug they are given could be removed from that regimen and put on a potentially more effective drug.

**Have you moved onto a new position or made a transition or advancement in your career since receiving this award?**

I recently started a tenure-track Assistant Professor faculty position in the Department of Structural Biology at Stanford University School of Medicine. The DoD BCRP award was instrumental in my development as an independent researcher as it provided me with the freedom to explore the research I was truly interested in and the opportunity to present my research at the Era of Hope conference, where I met multiple future collaborators and expanded my professional network. The Era of Hope conference also provided a great platform to interact with breast cancer advocates, which gave meaning to my work and motivated much of my research.
Probing the Molecular Basis of Cell-Matrix Mechanical Signaling in 3-D Breast Tumor Models with Multiphoton Microscopy
Kandice Tanner, Lawrence Berkeley National Laboratory
FY08 Postdoctoral Award

Complete understanding of both cell mechanobiology and interaction with the cell microenvironment is vital to unraveling how normal cells transform into malignancies. Dr. Kandice Tanner is studying the mechanics by which breast cancer cells develop into and maintain mammary tissues and how corruption of that process contributes to malignant transformation. Dr. Tanner talks about the BCRP-funded research she performed during her postdoctoral training:

**What research question did you address?**
Healthy breast epithelial cells form either sphere-shaped structures known as acini or tube-shaped ducts. Polarity (spatial orientation) of cells in the acini is essential for the health and well-being of the breast, and loss of this polarity as a result of cells not forming spheres is one of the earliest signs of malignancy.

We asked a fundamental question: “How are epithelial cells able to assemble into spheres that are similar in size and shape” or, essentially, “how does a cell know which way is up?” To answer this, we used an in vitro system developed in the lab of Dr. Mina Bissell. This cell culture recapitulates the role of epithelial tissue polarization in the human breast, both in normal tissue and in cancer development. Using nonmalignant HMECs we observed a novel behavior wherein HMECs undergo multiple rotations in 3-D laminin-rich extracellular matrix to form spherical acini. When we perturbed this spinning movement, which we called coherent angular motion (CAMo), spherical structures could not develop. Disruption of this rotation caused HMECs to form aggregates similar to those observed for malignant breast epithelial cells. We then observed cancer cells in this system and confirmed that they do not display CAMo but instead undergo random uncoordinated motility.

**Who contributed to this work?**
This work was made possible by the combined strength of the interdisciplinary teams where physical scientists bring a fresh perspective and address a biologically relevant question. Often, there is a lack of dialogue between the two respective fields of physical scientists and biologists. It was crucial that we had the appropriate in vitro cell culture system that recapitulates the transition from nonmalignant to malignant phenotypes seen in vivo.

**How will this discovery benefit breast cancer patients?**
We postulate that this cohesive CAMo motility is the mechanism by which the original structure of the breast tissue is restored following lactation and breast feeding. It follows that if this process is corrupted and the breast architecture is malformed, this may create a tissue environment more permissive for tumor formation.

We expect that studies based on this finding will yield a new understanding of how normal and cancer cells are affected by their microenvironments, leading to novel cancer therapies and new concepts in malignancy, metastasis, and drug resistance.

**How did this award help you advance in your career?**
This award was critical for my success. As a classically trained physicist, I was given the opportunity to make meaningful contributions in breast cancer. It allowed me to fully immerse myself in a cancer biology lab and obtain a better understanding of how my training can address biological questions that can have a significant impact on cancer. During my search for a faculty position, I found this prestigious postdoctoral award was noted by the selection committees as demonstrative of excellence. Ultimately, I was selected as a Stadtman investigator at the National Cancer Institute (NCI). The goal of my lab is to integrate concepts from molecular biophysics and cell biology to understand how cells and tissues sense and respond to their physical microenvironments and to exploit these principles for the design of effective therapeutics.

Montage of micrographs showing that nonmalignant cells rotate during early acinar morphogenesis where one revolution is completed in ~1 hour. Green delineates the nuclei (H2B-GFP) and red indicates F-actin (mCherry LifeAct).
Breast cancer frequently metastasizes to the bone of the spine where it can cause tremendous pain and neurological complications severely diminishing quality of life. Under the mentorship of Drs. Gang Zheng and Brian C. Wilson, Ms. Tracy Liu is developing a novel photodynamic therapy (PDT) for the treatment of breast cancer metastases to bone. PDT uses light and light-activated drugs to kill tumor cells. To improve the specificity of PDT, Ms. Liu plans to develop a new generation of photosensitizers she calls “photodynamic molecular beacons” (PMBs), which will exploit the overexpression of matrix metalloproteinases (MMPs) on the surface of metastatic breast cancer cells. When administered, PMBs are inert; they can be “switched on” to kill breast cancer cells by the simultaneous action of MMPs and application of laser light at metastatic sites.

Using animal models of metastatic breast cancer, Ms. Liu has demonstrated that these PMBs can be targeted specifically to vertebral metastases and activated by MMP-expressing breast cancer cells with minimum uptake or activation in the normal bone and neurological (i.e., spinal cord) tissues surrounding metastatic sites, thus avoiding collateral neurologic damage. In addition, she has shown that when activated by light, the PMBs not only destroy spinal metastases but also destroy bone cells (osteoclasts) responsible for the weakening of bone seen in many patients with metastatic cancer. Thus, these smart PMBs have the potential to increase survival and improve the quality of life for patients suffering from breast cancer vertebral metastases.
Largazole, a Novel and Selective Anti-Breast Cancer Agent
Xuedong Liu, University of Colorado, Boulder
Andrew Phillips, Yale University
FY09 Idea Award

Dr. Xuedong Liu and Dr. Andrew Phillips are exploring a novel concept in drug discovery, called dual-specificity inhibition. Dual-specificity inhibition involves the development of a single molecule capable of targeting multiple aberrant cell-signaling pathways and is a useful modality in breast cancer where multiple cellular pathways are perturbed leading to development of the disease. Targeting multiple pathways could significantly improve therapeutics specificity and lead to concentrated killing of cancer cells while leaving normal cells unperturbed.

Previously, Dr. Liu and colleagues found that largazole, a natural product isolated from a marine cyanobacterium, inhibits the growth of breast cancer cells without affecting normal breast epithelial cells. Molecular analysis of largazole showed that it inhibited both histone deacetylase and ubiquitin proteasome pathways, which are implicated in breast cancer. The researchers aim to improve the potency and selectivity of the compound by developing analogs of largazole and determining their chemotherapeutic efficacies in mice. Preliminary results from Dr. Liu’s research suggest that it is feasible to design novel dual inhibitors that are capable of targeting two or more aberrant signaling pathways in breast cancer, potentially increasing cancer cell specificity, as well as reducing toxicity associated with many treatments.

“The BCRP is one of the most integral breast cancer funding programs we have today. The researchers use innovative, challenging, ‘outside the box’ approaches in their research. It is wonderful to think that one or more of these proposals could actually change the face of breast cancer by halting the deaths from this disease and by bringing hope to those who are afraid they may be diagnosed next. Seven years and 14 surgeries after my diagnosis, I am a warrior in the fight against breast cancer. It’s so refreshing to know that my fellow advocates—especially the researchers—are fighting it with me.”

Frances Wand
Consumer Reviewer
Avon Foundation Community
Education and Outreach Initiative
Engineered Erythrocytes for Prevention of Dissemination of Metastatic Breast Cancer
Dmitri Simberg, University of California, San Diego
FY09 Idea Award

Metastatic lesions form when breast cancer cells escape the primary tumor and survive a journey through the circulatory system to colonize distant organs. Dr. Dmitri Simberg has developed engineered red blood cells (RBCs) to investigate how these events can be disrupted. The modified RBCs are coated with antibodies against markers of circulating metastatic cells. Consistent with the nature of healthy RBCs, these modified RBCs are then capable of deforming and squeezing through the smallest blood vessels within the vasculature to react with a tumor cell in the circulation. Experimental results have demonstrated that RBCs can be effectively modified, reinjected into animal models, and sustain long circulating properties (>3 days half-life). Furthermore, upon targeting, robust binding and efficient transfer of molecules from RBCs to tumor cells have been demonstrated in vitro and in vivo. Ongoing investigations include loading RBCs with therapeutic molecules and testing antimetastatic effects in a mouse model of metastatic breast cancer. If shown to be successful, modified RBCs could be employed at different stages of the metastatic dissemination process for systemic therapy and hold the promise of rapid translation to the clinic.

Novel Technology for Rogue Cancer Cell Detection
Bahram Jalali and Dino Di Carlo
University of California, Los Angeles
FY09 Idea Award

Identification of circulating tumor cells (CTCs) in patient blood can be useful in determining prognosis and predicting possible relapse. Current gold standard techniques to isolate CTCs have low throughput and high statistical uncertainty, especially in early-stage disease. Drs. Bahram Jalali and Dino Di Carlo are developing an automated, flow-through, single-cell optical microscopy system that can evaluate, diagnose, and screen a large population of cells and detect rare cells with high specificity, sensitivity, and statistical accuracy in a short amount of time.

This system utilizes a unique integration of microfluidic technology for focusing and ordering flow of cells, a fast optical imaging modality known as serial time-encoded amplified microscopy for sharp imaging of cells in high-speed flow and hybrid optoelectronic image processing circuitry for real-time image processing. The system captures images of cells from the highly condensed microfluidic flow into a series of “E-slides”—an electronic version of glass slides—on which cells of interest are digitally imaged and analyzed. So far, the research team has demonstrated real-time identification and screening of rare MCF-7 breast cancer cells in blood samples from mice with an unprecedented throughput of 100,000 cells/sec and false positive rate of one per million. With only a simple blood draw from a patient, this device will enable critical early detection of occult breast cancer not currently detectable by standard screening modalities.
Improving External Treatments for Breast Cancer Tumors
Mahta Moghaddam, University of Southern California
Paul Carson, University of Michigan
FY09 Idea Award

Malignant tissues have properties that make them distinguishable from healthy tissue, including an ability to highly absorb microwave and ultrasound energy and thus be heated more quickly than surrounding tissue. This property can be exploited for thermal therapies in which elevated temperatures are used to achieve cell death or render the cells more vulnerable to ionizing radiation and chemotherapy. Both microwave and ultrasound modalities have been used for thermal therapies; however, there are limitations with each method. Drs. Mahta Moghaddam and Paul Carson are investigating the combination of two thermal therapies: high-intensity focused ultrasound (HIFU) and high-intensity focused microwave (HIFW). The proposed combined system seeks to remove the limitations inherent in individual application of these therapies.

Dr. Moghaddam is working to improve targeting the microwaves in HIFW to overcome focus and uniformity issues using an array design that could be fine-tuned for each patient. Dr. Carson is developing a transducer array that will allow placement of the HIFU focal zone close to the chest wall, enabling deep tumors to be treated at higher speed and uniformity than currently possible with ultrasound. Using information gathered from the study of each treatment modality, the collaborators aim to combine these therapies in a microwave-ultrasound synergistic thermal (MUST) treatment system. Experimental results using laboratory prototypes generated focused heating sufficient for an antitumor effect in tissue-mimicking gelatin phantoms. The heating focal spot sizes were as small as 1.5 cm with microwaves and 1.5 mm with ultrasound. Further development of the MUST system will capitalize on the strengths of each modality so that the combined system could substantially enhance treatment results through precise and uniform heating accompanied by simultaneous imaging of the temperature.
Developing Small RNA-Based Therapy to Target Breast Cancer Stem Cells
Judy Lieberman, Immune Disease Institute, Inc.
FY08 Idea Award

Small RNA sequences in cells, called microRNAs, bind to complementary sequences in messenger RNA and interfere with or silence gene expression. This natural mechanism of gene regulation is called RNA interference (RNAi). A new approach to cancer therapeutics involves the development of small interfering RNAs (siRNAs) that mimic microRNAs to suppress the expression of genes involved in cancer.

Dr. Judy Lieberman received funding to develop an RNAi-based therapy for triple-negative breast cancer (TNBC), an aggressive breast cancer subtype that is characterized by lack of estrogen, progesterone, and HER2 receptors. She observed that BPLER cells (human mammary progenitor cells) generate tumors that resemble TNBC in mice. Using an siRNA screen, Dr. Lieberman identified 154 genes that BPLER cells depend on for cell survival. The clinical relevance of these genes was then evaluated in human breast tumor cell lines. Some of these genes, including proteasome components, were shown to be highly expressed in TNBC and associated with poor prognosis. BPLER and basal-like TNBCs were highly and selectively susceptible to proteasome inhibition, suggesting a new therapeutic approach for the treatment of TNBC.

Characterization of the Antitumorigenic Effects of Strigolactone, a Novel Plant Hormone
Ronit Yarden, Georgetown University
FY10 Concept Award

Approximately 25% of the drugs used in breast cancer in the past 20 years have been plant-derived and, more recently, phytohormones—hormone-like substances produced by plants—have been evaluated for their ability to inhibit the growth and survival of human cancer cell lines. Strigolactones are a novel class of phytohormones, first identified as inducers of seed germination of the root of a plant known as striga. Dr. Ronit Yarden is examining whether strigolactone analogs exert an inhibitory effect on the growth and survival of human breast cancer cells, normal breast epithelial cells, and cancer stem cells (CSCs).

Dr. Yarden has found that strigolactone GR24 and several of its chemical analogs are potent inhibitors of mammalian cancer cell growth in vitro. Her studies have shown that strigolactones act by inhibiting cell cycle progression of cancer cells, causing cell cycle arrest in estrogen receptor (ER)-positive breast cancer cells with intact tumor suppressor p53 and inducing apoptosis in ER-negative breast cancer cells with mutant p53. Furthermore, strigolactones have minimal effects on normal breast epithelial cells. She has also discovered that strigolactones inhibit the formation and growth of mammospheres, a specialized aggregate of cells rich in CSCs. Inhibition of CSCs is an important therapeutic goal, as these cells are believed to regenerate the tumor and cause recurrence. Taken together, Dr. Yarden’s study indicates that strigolactones represent a new class of plant-derived drugs to treat breast cancer.
Many breast cancer therapies in clinical use inflict off-target damage to healthy tissues and cells. Dr. Ron Weiss is focusing his efforts on developing a new way to target and destroy only cancerous cells, leaving other cells unaffected. He has been exploring the use of RNAi-based “logic circuits,” contained within the cells themselves. The logic circuit consists of an apoptotic (cell killing) gene, an siRNA that can bind to and degrade the gene, and a set of additional short messenger RNA sequences called mStaples that bind to both cancer biomarkers and the killer gene but have a higher affinity for biomarkers. In normal cells with low cancer biomarker levels, the mStaples are plentiful and will bind to the killing gene, which permits the siRNA to bind to and degrade the gene. In cancer cells, where the biomarker level is high, most of the free mStaples will be bound to the cancer biomarker; therefore, the siRNA cannot bind the apoptotic gene, which is then expressed, resulting in the death of the cancer cell.

Dr. Weiss demonstrated that the individual components of the logic circuit function within cells, including the suppression of genes like the apoptotic gene and recognition-specific cancer biomarkers. He then introduced the individual components into a mixed population of cells, wherein only one cell type expressed the biomarker designed to initiate expression of the apoptotic gene. Dr. Weiss found that the system led to the death of the targeted cell population with high specificity. With this initial success, Dr. Weiss has begun work toward eventual clinical deployment of the proposed system by packaging all of the necessary components of the logic circuit into a single expression vector capable of being introduced into humans.
Development of Laser-Mediated Nanodroplet Real-Time Reverse Transcriptase PCR on Circulating Tumor Cells
Richard Cote, University of Miami Miller School of Medicine FY11 Idea Expansion Award

CTCs found in the peripheral blood of patients with cancer can be used to determine prognosis and monitor therapeutic response and disease recurrence. However, detection and analysis of CTCs are costly and labor intensive, requiring specialized laboratories and expertise. Dr. Richard Cote, in collaboration with Dr. Gregory Faris of SRI International, is developing a CTC detection system, expanding work initially supported by his FY08 Synergistic Idea Award with Dr. Changhuei Yang, of the California Institute of Technology.

Initial tests show that the novel device, which uses a parylene membrane microfilter, captured CTCs with >90% efficiency while maintaining a high throughput. Through the collaboration with Dr. Yang’s group, a microscope system capable of imaging tumor cells on the microfilter was developed as a prototype to the final product, a holographic scanning microscope.

Through the collaboration with Dr. Faris’ laboratory, Dr. Cote proposes to enhance the ability of the microfilter device to capture and characterize CTCs in real time. This will be accomplished through integration of a novel platform that uses laser heating to conduct real-time reverse transcriptase polymerase chain reaction, thus allowing efficient point-of-care analysis of individual CTCs trapped by the microfilter, with no impact on the surrounding hematopoietic cells.

The work of Dr. Cote and his collaborators shows promise for a cost-effective, easy-to-operate device that would enable physicians to detect and initiate treatment for early metastasis and improve therapeutic monitoring.

“Since being diagnosed with breast cancer, I have tried to find ways to turn that negative experience into a positive. The BCRP’s collaboration between breast cancer survivors and scientists to fund innovative and impactful research is one of the most positive post-breast cancer experiences I have had.”

Tracy Leduc
Consumer Reviewer
Annie Appleseed Foundation
Development of Technologies for Early Detection and Stratification of Breast Cancer
David Walt, Tufts University
FY10 Innovator Award

Biological markers of disease can only be detected when concentrations rise to or above the detection limit of standard analytical methods. Given the ultrasensitive, single-molecule techniques that have come out of the genomics era, the ability to identify and measure proteins, metabolites, or genetic makeup at concentrations far below the sensitivity of traditional immunoassays or imaging modalities is now within reach. Dr. David Walt, a distinguished professor and founder of a genetic analysis company that is a leader in the global market, is dedicating his efforts to developing and applying ultimate high-sensitivity and high-resolution technologies to understanding breast cancer. His goal is to employ ultrasensitive techniques to discover new biomarkers within serum, thus enabling implementation of a simple blood test for diagnosing breast cancer. He predicts that the ability to follow the appearance of a single molecule will enable early detection while monitoring disappearance, such as markers that disappear after chemotherapy, radiotherapy, or surgical removal of the tumor, will enable assurance that the tumor has been eliminated. Technologies previously developed by Dr. Walt’s laboratory have transformed the fundamental understanding of biochemistry and have demonstrated a successful transfer of knowledge to the clinic. This innovative approach to understanding breast cancer holds great promise for the development of diagnostic methods for early diagnosis and treatment.

During the first year, Dr. Walt and his team successfully identified candidate biomarkers based on prior associations with breast cancer progression. They went on to develop ultrasensitive assays, including digital ELISA (enzyme-linked immunosorbent assay) and various microRNA (miRNA) platforms, for several of these new markers. Results have shown remarkable potential with regard to the level of detection, and application in human-in-mouse models is being investigated. Further optimization to reduce background, increase reproducibility, and increase assay efficiency is under way. Once suitable candidate biomarkers have been validated, prospective patient studies will be initiated to test whether these assays are useful for early-stage breast cancer diagnostics and for predicting tumor aggressiveness. This characterization of breast cancer samples, with single-cell resolution, may allow discovery of new indicators with diagnostic value and holds the promise of a better informed approach to therapy.
Escape from Tumor Cell Dormancy
Alan Wells, University of Pittsburgh
Linda Griffith, Massachusetts Institute of Technology
FY03 Idea Award and FY09 Idea Expansion Award

Metastatic cells can escape the primary breast tumor and lie dormant in distant organs for years. The triggers for the “re-awakening” of these micrometastases are not understood. The liver is a major site of metastatic spread for breast cancer. To understand which tumor cell behaviors contribute to metastasis and disease progression, Dr. Alan Wells collaborated with Dr. Linda Griffith to develop a 3-D ex vivo organotypic liver tissue system to study tumor metastasis. This bioreactor system allows liver cells to grow in a device outside of the body while preserving and recreating the behaviors of normal cells, mimicking normal liver physiology. The device was used to examine factors that stimulate the growth of breast cancer cells that spread to and remain dormant in the liver.

The bioreactor system enabled the study of the transition of breast cancer cells from a dormant, nonproliferative state to one where the cancer cells were actively dividing and growing. Factors that were studied included the microenvironment of the liver, including production of growth factors and cytokines. Cancer cells produce inflammatory cytokines that can cause liver cells to lose their close attachment to each other, making a niche for the tumor cells to reside. The tumor cells can remain in a state of dormancy until activation of the cancer cells occurs. The activation events will be the focus of future study, leading to identification of potential targets for therapy, both to eliminate the dormant cancer cells and to prevent their renewed growth. Drs. Wells and Griffith and their teams have successfully formed partnerships with two companies in the private sector, Draper Laboratories and Zyoxel, to continue this work.

Current reactor design recapitulates liver tissue with 3-D structure and perfused flow.
A Noncoding Transcript RNA and Its Role in the Development of Breast Cancer
David Smith, Mayo Clinic and Foundation, Rochester, Minnesota
FY06 Concept Award and FY09 Idea Award

Most of the focus in breast cancer genetics has been on specific protein-coding genes whose alteration either predisposes a patient to, or is involved in, breast cancer development. Surprisingly, though most of the human genome is transcriptionally active, less than 2% is involved in coding for proteins; therefore, noncoding RNA transcripts vastly exceed protein-coding transcripts. Dr. David Smith has identified a group of 12 long stress-responsive noncoding transcripts, termed LSCINCTs, that appear to be involved in breast cancer cell proliferation.

Dr. Smith has characterized the expression of one of these noncoding genes, LSCINCT5, and has shown that breast tumors express higher levels of this RNA compared with normal breast tissue. Reducing the expression of LSCINCT5 in breast cancer cells using an “antisense oligonucleotide” molecular technique resulted in a decrease in the proliferation of cells and change in the expression of 96 protein-coding genes in these cells. These findings suggest that LSCINCT5 has a regulatory role in breast cancer. The potential impact of these studies is that regulatory noncoding RNA transcripts such as LSCINCT5 may be just as important as the protein-coding genes associated with breast cancer and may represent a novel target for development of breast cancer therapeutics.

Dynamic Testing of Signal Transduction Deregulation During Breast Cancer Initiation
Victoria Seewaldt and Tuan Vo-Dinh, Duke University
FY08 Synergistic Idea Award

In the past several decades, researchers have identified numerous genetic and physiological factors that influence breast cancer risk. However, current techniques for early detection of breast cancer are not optimal. Mammography, the standard screening modality for breast cancer, is less effective at detecting lesions in premenopausal women, who account for a disproportionately large number of high-risk patients; MRI screening is expensive and frequently not covered by insurance.

The Duke High Risk Clinic, headed by Dr. Victoria Seewaldt (pictured with a patient), is researching more accurate and individualized approaches in breast cancer detection. Serial random periareolar fine needle aspiration (RPFNA) performed on asymptomatic patients seen at the clinic to test for precancerous changes is aimed at identifying the molecular signature of breast cancer initiation. Acting on the hypothesis that dysregulation of protein phosphorylation signaling occurs during breast cancer initiation, Dr. Seewaldt and colleagues performed proteomic profiling on live breast cells collected by RPFNA in a pilot study that confirmed that different patterns of protein phosphorylation were found in cytologically abnormal mammary cells from high-risk patients. Concurrently, Dr. Tuan Vo-Dinh developed surface-enhanced Raman-scattering active fiber optic nanoprobes capable of sensing target molecules in single living cells collected by RPFNA. The researchers are combining their expertise to build a nanoprobe that will detect protein phosphorylation changes suspected in the earliest stages of breast cancer in RPFNA samples. Successful development of this nanoprobe offers a potentially more reliable and accurate alternative screening option for early detection of breast tumors in high-risk individuals.
Therapeutic Targeting of Breast Cancer with Metastasis Suppressor MicroRNAs
Sohail Tavazoie, Rockefeller University
FY09 Era of Hope Scholar Award

One of the key factors contributing to the survival of patients with breast cancer is whether the cancer cells attain the ability to metastasize to other organs. Metastatic progression is a complex, multistep process, which makes predicting, preventing, or treating it very difficult. Dr. Sohail Tavazoie is investigating whether specific miRNAs can suppress metastatic progression, as well as suppress the growth of established metastases.

Dr. Tavazoie silenced the expression of miR-126, a noncoding miRNA, in human breast cancer cells in mice and found increased metastatic colonization in several organ systems including lungs, brain, and bone. Restoring expression of miR-126 resulted in the formation of fewer metastatic nodules. Furthermore, Dr. Tavazoie observed that metastases in mice where miR-126 was silenced showed increased endothelial and blood vessel density and that suppression of miR-126 in cell culture increased recruitment of endothelial cells, an essential process for new blood vessel formation. Taken together, these results show that miR-126 acts to suppress metastatic initiation and colonization and that silencing of miR-126 enhances both formation and progression of metastases.

Using transcriptome analysis, Dr. Tavazoie identified eight genes that are suppressed by miR-126 and found that patients whose primary breast cancers overexpressed these genes were more likely to develop metastases. These metastases also occurred sooner than metastases in other patients with breast cancer. From these findings, Dr. Tavazoie concluded that miR-126 works, in part, by suppressing expression of these eight genes, which represent new targets for therapeutic interventions to prevent breast cancer metastases.
A New Therapeutic Paradigm Exploiting Low-Dose, Estrogen-Induced Apoptosis
V. Craig Jordan, Georgetown University
FY05 Breast Cancer Center of Excellence Award

Despite significant advancements made in treating ER-positive breast cancer, the majority of patients eventually become unresponsive to treatments targeting the ER because their tumors acquire resistance. Dr. V. Craig Jordan—whose seminal work in the development of tamoxifen and raloxifene led to game-changing treatment and prevention of estrogen-dependent breast cancer—discovered that low-dose, short-term estrogen treatment causes apoptosis in antihormonal-resistant breast cancer cells. Using an interdisciplinary approach, Dr. Jordan is translating this discovery into a clinical solution for ER-positive breast cancer. He has created a consortium core to coordinate multi-institutional clinical trials evaluating the efficacy and dose response of proapoptotic effects of the estrogen Estrace in patients following the failure of antihormonal therapies. Patient accrual is currently ongoing.

The research team is also elucidating the molecular mechanisms of estrogen-induced survival and apoptosis in breast cancer cells resistant to either selective ER modulators or long-term estrogen deprivation. Key components of the ER signaling pathways that regulate survival and apoptosis have been identified, including caspase 4 as the trigger caspase and AIB1 (amplified in breast cancer-1) as the controlling mechanism that initiates estrogen-induced apoptosis in antihormone-resistant cancer cells. Dr. Jordan’s team is the first to report on the post-translational regulation of prohibitins as ER corepressors, providing important insight into potential targets for therapeutics. A novel discovery—c-Src inhibitors actually block estrogen-induced apoptosis—suggests that clinically available c-Src inhibitors should not be used to treat patients with breast cancer who have become resistant to antihormones. Shape and conformation of the ER complex within a cell also play a role in triggering estrogen-induced apoptosis. Whereas planar estrogens (class I) produce a neat complex, nonplanar estrogens (class II) do not. Rather, they prohibit ER from closing around its ligand, thereby blocking estrogen action.

Taking these and other findings into account, another major accomplishment was the creation of a “map” that depicts the life and death of breast cancer cells in response to physiological estrogen. Dr. Jordan’s group, using novel methodology it developed and termed dAUC analysis (differential area under the curve analysis), identified both estrogen-stimulated and estrogen-independent regulated genes across time. The identified genes may serve as biomarkers to predict response to estrogen therapy or provide the basis for improving clinical response rates to estrogens given in combination with other agents.
Strategies for Personalized Treatment of Metastatic Breast Cancer: Vascular Normalization and Sensitization
Rakesh Jain, Massachusetts General Hospital, Boston
FY09 Innovator Award

Tumor vessels are structurally and functionally abnormal, limiting the effectiveness of various treatments. Dr. Rakesh Jain is investigating two complementary strategies to target the tumor blood vessels and improve treatment outcome in metastatic breast cancer.

The first strategy, called vascular normalization, involves restoring normal function to abnormal tumor blood vessels and microenvironment, thereby improving the delivery and efficacy of therapeutic agents to kill tumor cells. Dr. Jain has investigated vascular normalization following inhibition of key molecules, such as vascular endothelial growth factor (VEGF) and transforming growth factor beta (TGFβ), in breast cancer models in mice. Vascular normalization caused by VEGF receptor inhibition was shown to increase the efficacy of antitumor vaccines by reprogramming the tumor microenvironment from immunosuppressive to immunostimulatory in conjunction with enhanced cytotoxic T-cell recruitment and activity. Furthermore, not only blood vessels but also interstitial matrix normalization can potentiate breast cancer treatment. For example, Dr. Jain showed that inhibition of TGFβ normalizes both blood vessels and interstitial matrix and hence improves delivery and penetration of the cytotoxic agents in tumors.

The second strategy, vascular sensitization, involves pretreating or priming tumor blood vessels with an antivascular agent followed by treatment with cytotoxic agents, resulting in the destruction of both the blood vessels and the tumor. Using high-throughput drug screening, Dr. Jain and coworkers also identified dehydro-α-lapachone (DAL) as possessing potent antivascular activity. DAL was shown to induce vascular pruning and delay blood vessel outgrowth in mouse mammary tumors. Moreover, combining an anti-VEGF agent with anti-HER2 drugs led to three- to fivefold increases in survival in mice bearing HER2-dependent breast cancers in the brain. These beneficial effects were due to pronounced antivascular effects and tumor necrosis and form the basis of a planned clinical trial on the treatment of brain metastasis—an unmet need—in patients with HER2+ breast cancer.

Dr. Jain’s innovative studies are leading to a better understanding of how to target the tumor vasculature and develop new strategies for treating metastatic breast cancer that has become resistant to other therapies.
Racial Disparities in the Initiation and Intensity of Adjuvant Therapy for Breast Cancer
Alfred Neugut, Columbia University
FY04 Breast Cancer Center of Excellence Award

Among the most important advances in breast cancer treatment has been the use of adjuvant radiation, chemotherapy, and hormonal therapy. Substantial increases in breast cancer survival have been realized with these lifesaving therapies but, for reasons not fully understood, some women do not initiate or fail to complete the full course of treatment. Differences in breast cancer survival between black and white women exist, and this racial disparity may be due in part to differences in the receipt of optimal adjuvant therapy. Drs. Alfred Neugut, Dawn Hershman, and Grace Hillyer of Columbia University in New York, along with a team of top scientists from across the country, are conducting a long-term cohort study, the Breast Cancer Quality of Care Study (BQUAL), to investigate the causes of noninitiation, nonadherence, and early discontinuation of adjuvant chemotherapy and hormonal therapy.

Since 2006, 1,156 women newly diagnosed with invasive breast cancer, approximately 15% of whom are black, have been enrolled in this study from three recruitment sites (New York, metropolitan Detroit, and northern California). To elucidate potential factors that contribute to poorer survival outcomes and to identify women less likely to undergo full treatment, participants were asked to complete several telephone interviews over the course of their treatment that covered topics such as their medical experiences, cognitive factors, emotional factors, and social relations. Further, participants were asked to provide a biological sample for DNA testing, and the treating physicians of study participants were queried about patient-physician communication and beliefs relating to shared treatment decision making.

Initial results have begun to unravel the reasons that some women undergo recommended adjuvant treatment and some refuse. Approximately 16% of women with hormone-sensitive breast cancer did not initiate adjuvant hormonal therapy. An analysis of the psychosocial factors influencing this noninitiation among study participants with hormone-sensitive breast cancer showed that those who had high-quality patient–physician communication, who felt the decision to start this treatment was an easy one to make, or who had positive beliefs about the efficacy of hormonal treatment were more likely to initiate hormonal therapy. Among those who refused adjuvant chemotherapy, noninitiation of therapy was associated with older age, more negative beliefs about treatment efficacy, fewer positive beliefs about chemotherapy, and heightened expectations for adverse side effects, particularly nausea. No racial disparities were observed in these two sets of analyses.

While analysis of disparity data is still ongoing, BQUAL results to date underscore the importance of physician–patient interaction in educating newly diagnosed women regarding the benefits of adjuvant therapy to increase its initiation and compliance.

“The DoD BCRP is always expecting the funded research to make a difference in the mission to end breast cancer. Those of us who review proposals must be critical thinkers, ask continually if this particular proposal is simply more of the same and incremental, or if it holds the possibility of real progress.”

Maria Wetzel
Consumer Reviewer
Michigan Breast Cancer Coalition
Defining Treatments for Triple-Negative Breast Cancer
Michael Lee, Massachusetts Institute of Technology
FY09 Postdoctoral Fellowship Award

Dr. Michael Lee is investigating the potential efficacy of combination therapies that generate DNA damage and inhibit the EGFR, which is overexpressed in many TNBCs. Simultaneous administration of this combination therapy for TNBC has been tested in preclinical studies and clinical trials previously, but the results to date have not shown a consistent, strong effect. Under the mentorship of Dr. Michael Yaffe, Dr. Lee is using a computational biology approach to investigate how the timing of drug delivery might improve this treatment modality.

Using high-throughput techniques on a panel of TNBC cell lines, Dr. Lee found that initial treatment with the EGFR inhibitor erlotinib 4 to 24 hours before treatment with doxorubicin (a DNA-damaging agent) was consistently synergistic in inducing cell death in several TNBC cell lines. To unravel the mechanism that makes this combination treatment time-dependent, Dr. Lee measured changes in cell-signaling networks, gene expression profiles, and cell-phenotypic responses and generated a mathematical model to further inform these treatment studies. He found that sustained EGFR inhibition increased susceptibility to cytotoxic agents by dynamically rewiring cell-signaling pathways that confer abnormal survival to cancer cells. Dr. Lee's approach to breast cancer physiology using computational biology may be key to discovering new modes of treatment among those previously regarded as ineffective.

Epigenetic Regulation of MicroRNA Expression: Targeting Triple-Negative Breast Cancer
Bridgette Collins-Burow, Tulane University
FY08 Concept Award

There is a need to identify therapeutic targets and treatment strategies for TNBC, an aggressive phenotype associated with rapid progression and poor outcomes. Dr. Bridgette Collins-Burow is evaluating whether treating TNBC cells with HDAC inhibitors causes increases in miRNA levels that can regulate the transition of epithelial to mesenchymal cells, a process that directs cancer progression and may have a role in aggressive breast cancers. She has identified miRNAs regulated by HDAC inhibitors that may be involved both in epithelial-to-mesenchymal transition and metastasis regulation. Dr. Collins-Burow has also observed that treatment with HDAC inhibitors prevented cell migration in TNBC cell lines and increased E-cadherin protein expression, indicating that it might be possible to reverse the epithelial-to-mesenchymal transition phenotype. Combined, these results indicate that HDAC inhibitors should be studied further as possible therapeutic options for this disease.
Targeting the REST Network in Triple-Negative Breast Cancer
Kristen Meerbrey, Baylor College of Medicine
FY09 Predoctoral Traineeship Award

Molecular targeted therapies have improved survival in patients with ER+ and HER2+ breast cancers; however, there are no effective targeted treatments for patients with ER-, PR-, and HER2- breast cancer (TNBC). RE1-Silencing Transcription Factor (REST) has been shown to act as a tumor suppressor in normal epithelial cells. REST protein has also been shown to be absent in TNBC, implicating its role in cancer initiation and proliferation. Under the co-mentorship of Drs. Thomas Westbrook and Jeffrey Rosen, Ms. Kristen Meerbrey is investigating the cell-signaling pathways involved in the regulation of REST to determine if these pathways are potential therapeutic entry points for TNBC.

Using RNAi-based screening, Ms. Meerbrey identified kinases and phosphatases involved in the degradation of REST in TNBC. Ms. Meerbrey discovered that SCYL1, TEX14, and PLK1 form an intramolecular complex (the STeP complex) that physically interacts with REST to regulate REST abundance in TNBC. She also discovered that REST is degraded during spindle assembly checkpoint (SAC) arrest, a critical checkpoint for maintaining chromosomal integrity during cell division, in a STeP complex-dependent manner. Surprisingly, REST also localizes to the spindle and midbody along with the STeP complex members in mitotic TNBC cells, suggesting REST has novel nontranscriptional functions in TNBC. Ms. Meerbrey’s work has identified the STeP complex that regulates REST abundance during prolonged SAC activation. The STeP complex may be a new point of therapeutic intervention in REST-deficient TNBC.

Development of a Vaccine Targeting Triple-Negative Breast Cancer
Denise Cecil, University of Washington
FY09 Postdoctoral Fellowship Award

Dr. Denise Cecil embarked on a promising career path in bench research when her mother’s breast cancer diagnosis spurred her to refocus on translational research with a goal of developing breast cancer therapies. Working in the laboratory of Dr. Nora L. Disis, Dr. Cecil identified insulin-like growth factor 1 receptor (IGF-1R) as a promising tumor antigen target for TNBCs and developed an IGF-1R vaccine. Mice implanted with triple-negative tumors and administered this vaccine showed significantly slowed tumor growth. Dr. Cecil found that the immune response stimulated by vaccination acted primarily through enhanced secretion of interferon gamma and the resulting shutdown of common cancer proliferation signaling cascades. She hypothesized that this mechanism of immune response might trigger “oncogenic shock,” a physiologic state in which tumor cells become more sensitive to a variety of anticancer therapies. As predicted, when normally tamoxifen-resistant mice were treated with the IGF-1R vaccine, they were sensitized to tamoxifen and showed a synergistic decrease in tumor growth in response to the combination therapy. With these promising results, the research team is close to manufacturing a human IGF-1R vaccine and designing a clinical trial to test the vaccine in patients with TNBC. Dr. Cecil’s research is truly satisfying her desire to “put a human face to… bench work and be encouraged by the thought of directly helping the women affected by the disease.”
H. Kim Lyerly  
FY11 Clinical Translational Research Award  
Developing an HER3 cancer vaccine to provide an effective therapy for endocrine-resistant patients and to eliminate the emergence of endocrine-resistant cells

Andrei Goga  
FY11 Era of Hope Scholar Award  
Identifying and validating new approaches to target the MYC oncogene, which is overexpressed in triple-negative breast cancer

Eduard Chekmenev  
FY11 Era of Hope Scholar Award  
Developing a novel approach for screening and monitoring response to treatment using subsecond molecular resonance imaging and hyperpolarized contrast agents

Peter Lee  
FY11 Era of Hope Scholar Expansion Award  
Developing integrated immunotherapy that targets multiple phases of the immune response for long-term effectiveness

Keith Knutson  
FY11 Idea Award  
Educating normal breast mucosa to prevent breast cancer development

Doris Germain  
FY11 Idea Award  
Delineating the key proteins that regulate pregnancy-associated breast cancer and could represent novel biomarkers for early detection and treatment

Steven Dowdy  
FY11 Idea Award  
Transforming RNAi technology by shrinking the current size of siRNA therapeutics by 5,000-fold and developing cell-permeable, monomeric molecules for better therapeutic delivery

Ulrich Bickel  
FY11 Idea Award  
Investigating a T-cell receptor mimic antibody with antitumor activities, capable of crossing the blood-brain barrier to treat cerebral breast cancer metastases

Salman Hyder  
FY11 Idea Award  
Delineating the multifunctional effects of a cholesterol inhibitor on degrading “bad” estrogen receptors (ER-α) while increasing the levels of “good” estrogen receptors (ER-β)
Clifford Dacso  
FY11 Idea Award  
Conducting an innovative translational epidemiology study on the preventive effects of the antimalarial drug chloroquine on breast cancer risk

Flemming Forsberg  
FY11 Idea Expansion Award  
Investigating subharmonic imaging as a means to measure interstitial fluid pressure and improve monitoring of tumor responsiveness to chemotherapy

Geoffrey Wahl and Charles Perou  
FY11 Idea Expansion Award  
Using a novel embryonic mammary stem cell gene signature to improve human breast cancer diagnostics and therapeutic decision making

Gregg Semenza  
FY11 Impact Award  
Exploring novel therapeutic strategies to disrupt oxygen-regulated tumor homeostasis and glucose metabolism

Feng Wang-Johanning  
FY11 Impact Award  
Exploring a virus—human endogenous retrovirus K—found in breast tumors as a causative agent and a potential target for innovative immunotherapies

Joan Massague  
FY11 Innovator Award  
Dissecting the genetic and molecular regulation of latent metastasis toward discovering therapeutic targets

Josef Penninger  
FY11 Innovator Award  
Defining the role of RANKL/RANK in breast cancer; finding new essential breast cancer genes using fly and murine haploid embryonic stem cell technologies

Jae-Hyun Park  
FY11 Postdoctoral Fellowship Award  
Determining how the hypoxic tumor microenvironment influences chemoresistance through genomic profiling of cancer cells

Hilary Wade  
FY11 Postdoctoral Fellowship Award  
Defining complexities in the responses of breast cancer cells to low and high doses of progestins
In the Clinical Pipeline

**ErbB2/ErbB3 Bispecific ScFv (ALM) Antibody**

**Gregory Adams**

The BCRP supported preclinical studies to develop and test an engineered 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.

**Prone Radiotherapy**

**Silvia Formenti**

With BCRP support, Dr. Silvia Formenti conducted clinical trials to assess the efficacy of an accelerated, hypofractionated whole-breast radiation therapy designed to minimize the length of radiotherapy required after partial mastectomy in patients with ductal carcinoma in situ (DCIS). In this method, patients are treated in the prone position rather than in the supine 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.

**Molecular Breast Imaging**

**Carrie Hruska**

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 breast tissue, the BCRP funded work to evaluate the concordance of MBI with MRI 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 U.S. Food and Drug Administration (FDA)-approved MBI units are commercially available.

**E75 Her2-Derived Peptide Vaccine (NeuVax™)**

**Constantin Ioannides**

The BCRP supported a study that sought to identify cytotoxic lymphocyte-recognized epitopes on HER2-overexpressing human breast tumors, during which Dr. Constantin Ioannides together with Dr. Bryan Fisk discovered E75, an immunodominant HER2 peptide. The E75 peptide has since been developed into an immunogenic peptide-based vaccine under the commercial name of NeuVax (Galena Biopharma). NeuVax is now in Phase 3 clinical trials.

**Intracutal Techniques**

**Susan Love**

Most breast tumors appear to arise in the cells lining the milk ducts of the breast. With BCRP funding, Dr. Susan 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 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.

**HER2 Bi-Armed Activated T Cells**

**Lawrence G. Lum**

The BCRP supported preclinical studies on HER2 bi-armed activated T cells, which induces the development of “memory” antigen-specific cytotoxic T lymphocytes directed at Her2. This led to a Phase 1 clinical trial in women with Her2+ metastatic breast cancer, which indicated that the treatment infusions are safe and induced long-term antitumor responses. The Her2 bi-armed activated T cells are currently in Phase 2 clinical trials for treating breast cancer.

**Optical Spectroscopy**

**Nimmi Ramanujam**

Dr. Nimmi 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 (lumpectomy) 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.
**IDO Inhibitor**  
**George C. Prendergast**

Indoleamine 2,3 dioxygenase (IDO) is an enzyme that is commonly activated in breast cancer and is implicated in preventing the antitumor immune response by blocking T-cell activation. The BCRP supported 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. George C. Prendergast demonstrated that the D isomer of an IDO inhibitor called 1MT (D-1MT) has potent antitumor properties, and his group discovered IDO2, an IDO-related gene, as one of its molecular targets. D-1MT is now in clinical trials for breast cancer and other solid tumors.

**GM-CSF-Secreting Vaccine**  
**Leisha Emens**

Dr. Leisha Emens has developed a therapeutic granulocyte/macrophage colony-stimulating factor (GM-CSF)-secreting breast cancer vaccine to be used in combination with standard cancer therapies. Her preclinical data provided the basis for a clinical trial that tested vaccine-cyclophosphamide-trastuzumab combination therapy in women with stage IV metastatic HER2+ breast cancer. Clinical benefit, defined as complete or partial response to treatment (tumor shrinkage) or stabilization of disease (halted growth or spread), was present at 35% after 1 year. Early analysis showed that overall survival was 40 months, a significant improvement over the historical overall survival of 12 to 24 months for similar patients who received trastuzumab alone. Furthermore, the safety profile indicates minimal harmful side effects. Dr. Emens is continuing clinical trials on this vaccine in a larger breast cancer study, as well as expanding to similar immune-based strategies in other gynecological malignancies.

**HER2 Peptide-Based Vaccine**  
**Mary (Nora) L. Disis**

Dr. Nora L. Disis has developed a vaccine that, when concurrently administered with trastuzumab, strongly elicits an immune response to the growth factor receptor HER2, generating long-term tumor-specific immunity. The HER2 intercellular domain peptide vaccine was evaluated in a Phase 2 clinical trial in stage III and stage IV HER2+ patients with breast cancer concurrently receiving trastuzumab. Results of the trial indicated considerable improvements in relapse-free survival, as well as minimal toxicity and prolonged, robust, antigen-specific immune responses. The vaccine has been licensed commercially for further investigation.

**Targeting Autophagy to Eradicate DCIS**  
**Lance Liotta and Kirsten Edmiston**

Approximately one-fourth of women diagnosed with breast cancer have DCIS, a nonaggressive, malignant precursor form of breast cancer that is confined to the mammary duct. Although most DCIS lesions remain dormant and do not invade or spread to the lymph nodes, some lesions progress to eventually become invasive and metastatic. Currently, there are no methods to predict which DCIS lesions will become invasive and no therapeutic options to prevent the invasive phenotype. Drs. Lance Liotta and Kirsten Edmiston of Inova Fairfax Hospital tested the hypothesis that some DCIS lesions are preprogrammed with invasive properties and that the mammary duct microenvironment provides a unique niche for DCIS cell survival. Their findings indicated that autophagy may play a key role in regulating the emergence of DCIS invasive progenitor cells and that chloroquine is a potential new therapeutic for treating DCIS. They are now conducting a neoadjuvant clinical trial using chloroquine as a potential DCIS treatment to prevent progression to invasive breast cancer.

**DCIS lesions will become invasive and no therapeutic options to prevent the invasive phenotype.**
Breast Cancer Research Program

Making an Impact

Herceptin®
Dennis Slamon

Herceptin (trastuzumab) is a monoclonal antibody that targets HER2. HER2+ breast cancer accounts for approximately 25% of all breast cancers. The BCRP was instrumental in supporting preliminary 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

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, provides a range of risk assessment, screening, and preventive services.

PTEN
Michael Wigler

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.

**Sentinel Lymph Node biopsy**

*Douglas Reintgen and Kathryn Verbanac*

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 of the arm, 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 multicenter clinical trials to validate lymph node mapping and sentinel lymph node biopsy as an accurate method to predict the presence of disease in the axillary lymph nodes.

**ATLAS Clinical Trial**

*Richard Peto*

BCRP funds supported initiation of the Phase 3 clinical trial ATLAS (Adjuvant Tamoxifen Longer Against Shorter), the largest breast cancer treatment trial ever undertaken. Adjuvant tamoxifen is the first-line treatment for ER+ breast cancer in premenopausal women. The ATLAS trial examined whether 10 years of tamoxifen confers greater benefit than 5 years of tamoxifen. Results of the trial indicated that the risk of recurrence or death from breast cancer was reduced in women who took tamoxifen for 10 years versus 5 years.

**Three-Dimensional Culture Systems**

*Mina Bissell*

The BCRP supported the development of 3-D 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, 3-D culture models have enabled the elucidation of oncogenic and other cell-signaling pathways that are controlled by cell-matrix interactions. 3-D culture models are currently utilized across academic laboratories and by drug companies as screening assays to test for therapeutic response.

**Skp2 Oncogene**

*Michele Pagano*

Skp2 and p27 are genes involved in the regulation of the cell cycle. 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 patients with breast cancer. These findings contributed to the practice of Skp2/p27 immunohistochemical analysis as a prognostic test performed in clinical pathology laboratories.

**BrainMetsBC.org**

*Patricia Steeg*

Breast cancer advocates on this team-based award led the efforts to develop an online resource (BrainMetsBC.org) that provides the latest information about brain metastases. The website, which is available in English and Spanish, includes updates on current research, treatments, and clinical trials, as well as personal experiences written by patients.

**PALB2 Mutations**

*Bing Xia*

BCRP funding contributed to the discovery of PALB2, a BRCA2 binding protein. PALB2 and BRCA2 work together to mend broken strands of DNA, which helps to maintain the rate of cell growth. While BRCA1 and BRCA2 gene mutations are high risk factors for breast cancer, these mutations do not account for all familial breast cancers. Identification of mutations in the PALB2 gene indicates an approximate twofold increase in breast cancer susceptibility due to its inability to interact with BRCA2. A commercialized PALB2 genetic test is available for those with familial breast cancer.

**Digital Mammography and Breast Tomosynthesis**

*Laurie Fajardo and Daniel Kopans*

Digital mammography allows for an expanded detection range of x-ray signals than standard film mammography. The BCRP provided support to optimize technology and to conduct a multicenter clinical validation of digital mammography. The study demonstrated that digital mammography is superior to film mammography in detecting breast cancer in women with dense breast tissue, leading to a change in clinical practice. The BCRP also supported the development and clinical evaluation of digital breast tomosynthesis. This 3-D digital mammography tool offers an additional 3-D view to capture images for improved sensitivity. A tomosynthesis system is now FDA approved and commercialized for clinical use.