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 been responsible for managing over $11.7 billion since its inception through fiscal year 2017 (FY17). 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 evaluating applications, with both tiers involving dynamic interaction between scientists and disease survivors (consumers). The first tier of evaluation is a scientific peer review of the applications, measured against established criteria for determining scientific merit. The second tier is a programmatic review conducted by the Programmatic Panel, which is composed of leading scientists, clinicians, and consumers. The Programmatic Panel compares applications to each other and makes recommendations for funding based on scientific merit, potential impact, adherence to the intent of the award mechanism, relevance to program goals, and portfolio composition.

Breast Cancer Research Program

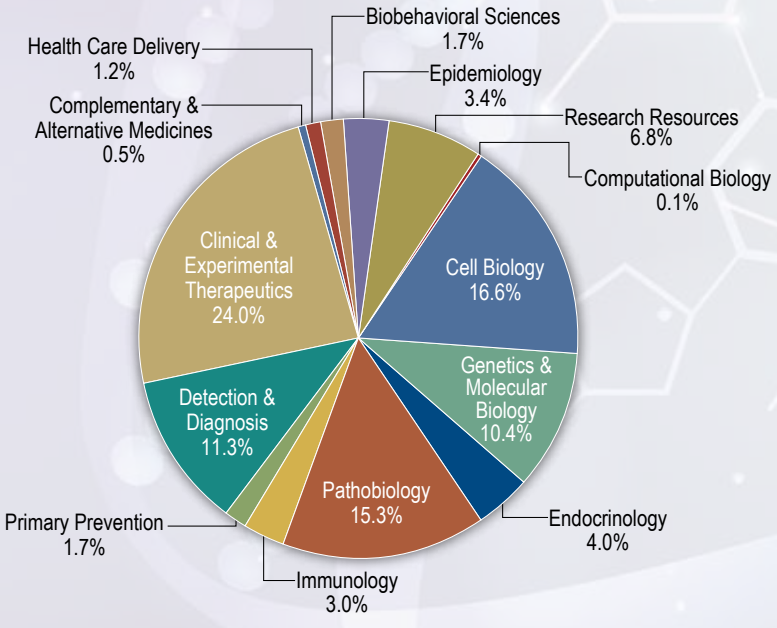
VISION: A world without breast cancer

MISSION: To end breast cancer for Service members, Veterans, and the general public by funding innovative, high-impact research through a partnership of scientists and consumers

ABOUT THE PROGRAM

The BCRP plays a leading role in the fight against breast cancer through its innovative approaches and its focus on research that will bring an end to this disease. The BCRP was established in 1992 as a result of the dedicated efforts of breast cancer advocates. Their continued efforts, in concert with the program's accomplishments, have resulted in more than $3.3 billion in congressional appropriations through FY17. The BCRP enables researchers to propose their best innovative ideas that address the urgent need to end breast cancer. Scientists are challenged to pursue high-risk, high-reward research, explore new paradigms that could lead to critical discoveries, and make an unprecedented impact on breast cancer. The BCRP also promotes synergistic collaborations across disciplines and integrates scientists and consumers in unique and meaningful research partnerships.

FY93–FY16 BCRP Portfolio

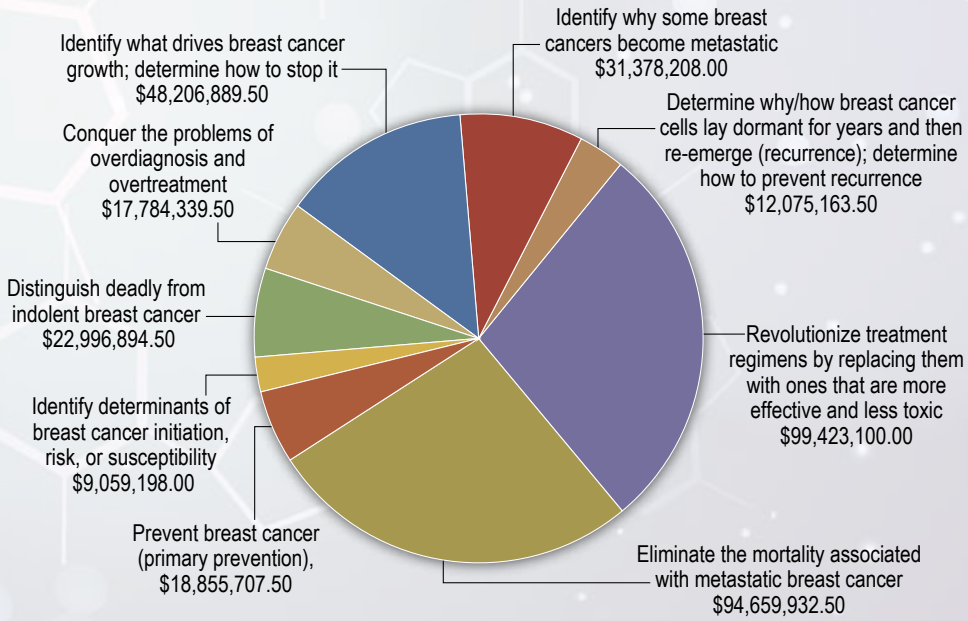


BCRP Overarching Challenges

Considering the current *Breast Cancer Landscape* and the BCRP's vision to end breast cancer, each application must address at least one of the following overarching challenges:

- Prevent breast cancer (primary prevention)
- Identify determinants of breast cancer initiation, risk, or susceptibility
- Distinguish deadly from non-deadly breast cancer
- Conquer the problems of overdiagnosis and overtreatment
- Identify what drives breast cancer growth; determine how to stop it
- Identify why some breast cancers become metastatic
- Determine why/how breast cancer cells lie dormant for years and then re-emerge; determine how to prevent lethal recurrence
- Revolutionize treatment regimens by replacing them with ones that are more effective, less toxic, and impact survival
- Eliminate the mortality associated with metastatic breast cancer

FY13–FY16 BCRP Funding Invested by Overarching Challenges



The Breast Cancer Landscape

The BCRP has prepared an overview of the *Breast Cancer Landscape*, covering the topics most pertinent to the program's mission of ending breast cancer.

Some key points from *The Breast Cancer Landscape*:

- Worldwide, breast cancer accounts for nearly a quarter of all cancers in women. In 2012, there were 522,000 breast cancer deaths globally.
- Evidence attributes the majority of breast cancers not to one single factor, but to various physical, environmental, and genetic factors.
- Most risk factors are not modifiable, including age, family history, BRCA mutation status, and breast density.
- Potentially modifiable risk factors, including obesity, use of combined estrogen and progestin menopausal hormones, alcohol consumption, smoking, and physical inactivity, are only weakly to moderately associated with breast cancer.
- An estimated 20-30% of women diagnosed with invasive breast cancer will have a recurrence.
- The rate of metastatic breast cancer at initial diagnosis in the United States has not changed since 1975.
- Treatments to permanently eradicate metastasis do not exist. There is no cure once metastatic disease has occurred.

Read *The Breast Cancer Landscape* at http://cdmrp.army.mil/bcrp/pdfs/bc_landscape.pdf.

Strategic Partnerships

Scientists and consumers working together to end breast cancer

"The DoD BCRP is a truly unique program that seeks to identify and support outstanding, cutting-edge research with a singular purpose – to eradicate breast cancer. Despite many important advances in research and treatment, breast cancer remains a challenging disease that affects the lives of countless individuals. To meet this challenge, we continue to require innovative strategies and interdisciplinary approaches that can prevent breast cancer altogether, as well as thwart its lethality due to advanced and metastatic disease. One of the greatest privileges in my career has been working with outstanding consumer advocates, scientists, and clinicians on the DoD BRCP Programmatic Review Panel, all of whom place the utmost important on scientific rigor and labor tirelessly toward this critical vision of ending breast cancer."

Jay Debnath, University of California, San Francisco
FY18 Programmatic Panel Chair

"Beyond my personal medical care provided by the military, it means so much to me that the DoD is also providing for military families by funding such important research on breast cancer and metastasis. I know that the program has resulted in current treatments like Herceptin®, and there are many others in the pipeline. Maybe one day, through the research funded by the DoD, more lives will be saved from this deadly disease. I am well aware that the research might not save me, but that is not going to stop me from fighting."

Alexis Rhoads, Military Spouse, Warriors 4 Warriors

Alexis passed away from metastatic breast cancer on October 29, 2017.

"I cannot overstate the importance of the DoD BCRP. It is one of the only federal grant programs that insist on including the patient's perspective in the review process through consumer advocates. The grants that come from the BCRP have funded some of the most important breakthroughs in breast cancer research, and they always consider the impact the research will have on actual patients in the real world, not just in the lab. The ripple effect that this has goes far beyond the DoD."

Andrea Hutton, Young Survival Coalition

"The DoD BCRP is critically important, because it is a major component in the efforts to expand survival, enhance quality of life, and save lives while increasingly working to put an end to this disease. As a consumer reviewer, I get to add another dimension of growth as an advocate for others who do and will travel through a journey with breast cancer until we reach that day."

Wanda Johnson, Reconstruction of a Survivor

Research Highlights

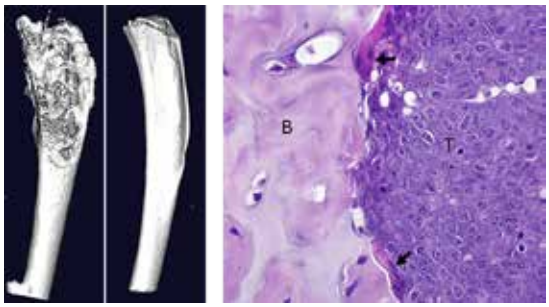
Alana Welm

Kelsi Andrade

RON kinase: A Target for Treatment of Cancer-Induced Bone Destruction and Osteoporosis

Alana Welm, Ph.D., University of Utah, FY07 Era of Hope Scholar Award; also pictured, Kelsi Andrade, Ph.D., University of Oklahoma Health Science Center

Dr. Welm and her team were able to elucidate a novel pathway that functions separately from receptor activator of nuclear factor κB ligand (RANKL) to promote bone loss in breast cancer patients, paving the way for a new clinically relevant therapeutic that could be used in combination with bisphosphonates and RANKL inhibitors to treat a large proportion of metastatic cancer patients. Dr. Welm was able to successfully show that inhibition of RON kinase function was both feasible and effective in reducing bone loss in mice injected with tumor cells expressing macrophage stimulating protein, a ligand for RON kinase. Only the bones of mice lacking expression of functional RON kinase, or given the RON kinase inhibitor, BMS-777607/ASLAN002, were protected from osteolysis. To test whether the in vivo findings were translatable into humans, plasma samples were obtained from a Phase I clinical trial (NCT01721148) of BMS-777607/ASLAN002 in metastatic cancer patients. Plasma samples from 13 of 21 treated subjects (62%) exhibited decreased β-cross-linked C telopeptide, a serum biomarker used to measure osteolysis, and an increase in bone-specific alkaline phosphatase levels, a biomarker of bone repair, after treatment with the RON kinase. BMS-777607/ASLAN002 was also found to be well tolerated by patients.



Left: MicroCT images demonstrating bone destruction in tumor-bearing tibia (left) compared to normal bone architecture in contralateral uninjected tibia (right) in a mouse model of bone metastasis.
Right: Bone-resorbing osteoclasts (arrows) at the interface of PyMT tumor cells (T) and bone (B) in mice.

Publication:

Andrade K, Fornetti J, Zhao L, et al. 2017. RON kinase: A target for treatment of cancer-induced bone destruction and osteoporosis. *Sci Transl Med* 9:1-11.

The Multifunctional Transcription Factor, TRIM25, Drives Breast Cancer Metastasis

Timothy A. Chan, M.D., Ph.D., Sloan Kettering Institute for Cancer Research, FY12 Era of Hope Scholar Award

Dr. Timothy Chan and his colleagues investigate genetic changes that regulate the metastatic progression of breast cancer in order to identify novel therapeutic targets for this disease and improve upon current diagnostics used for breast cancer. Dr. Chan and his team identified TRIM25, a multifunctional transcription factor, as a keystone protein in metastatic breast cancer. Of the 32 cancer types tested from The Cancer Genome Atlas (TCGA), TRIM25 was most frequently amplified in breast cancer, and elevated TRIM25 expression was significantly associated with poor outcome in the 1,038 TCGA breast cancer tumors analyzed. Dr. Chan and his team also elucidated the molecular mechanisms regulating TRIM25 and found that they are independent of hormonal status of the tumor cells. Other detailed analyses revealed TRIM25 as a master regulator protein that can influence multiple downstream transcription programs involved in the metastatic progression of breast cancer, as well as the maintenance of stemness for breast cancer tumor cells. Dr. Chan also showed that increasing or decreasing TRIM25 expression in triple-negative breast cancers (TNBC) cell lines resulted in increased or decreased lung metastases in a mouse model of breast cancer, respectively. This cutting-edge research conducted by Dr. Chan and his team highlights TRIM25 as a novel breast cancer therapeutic target.

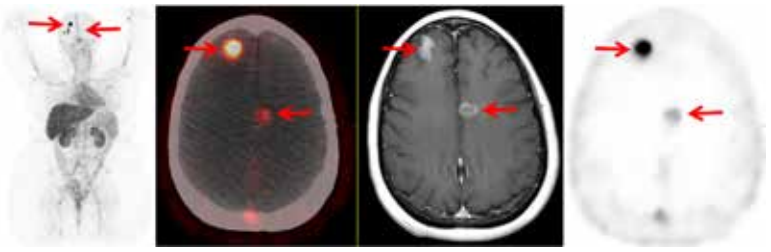
Publication:

Walsh LA, Alvarez MJ, Sabio EY, et al. 2017. An integrated systems biology approach identifies TRIM25 as a key determinant of breast cancer metastasis. *Cell Reports,* 20:1623-1640.

Detection of HER2-Positive Metastases in Patients with HER2-Negative Primary Breast Cancer

Gary A. Ulaner, M.D., Ph.D., Memorial Sloan Kettering Cancer Center, FY13 Breakthrough Award

In recent years, research has shown that HER2 expression at metastatic sites can differ from HER2 expression at the primary site in breast cancer patients. Dr. Ulaner and a team of researchers at Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College showed that 89Zr-trastuzumab could detect HER2-positive metastases in patients diagnosed with HER2-negative primary tumors, and that these patients responded to HER2-targeted therapies. Nine patients were enrolled in Dr. Ulaner's study, all of whom had been diagnosed with estrogen receptor-positive HER2-negative primary tumors and had at least one site of metastatic disease. Five patients showed evidence of HER2-positive metastases, and image-guided biopsy results confirmed HER2-positive status in two patients. Both of these patients responded to trastuzumab, pertuzumab, and paclitaxel, as well as concomitant taxane antimitotic chemotherapy. Dr. Ulaner also developed a second radiotracer that has just entered a Phase I clinical trial (NCT03109977) to try to improve the accuracy of the imaging procedure for diagnosing HER2-positive metastatic disease. This trial highlights the impact of HER2-targeted imaging on identifying patients that could benefit from systemic HER2-targeted therapy and may help physicians create individualized therapy to overcome tumor heterogeneity and improve patient outcomes.



Left: MIP image from a 89Zr-pertuzumab PET, demonstrating avid intracranial foci.
Left middle: Axial fused 89Zr-pertuzumab PET/CT through the brain, demonstrating foci localize to brain parenchyma.
Right middle: Axial T1 post gadolinium MR, demonstrates enhancing brain metastases, which correspond to the 89Zr-pertuzumab foci on PET/CT.
Right: Axial 89Zr-pertuzumab PET through the brain, demonstrating foci.

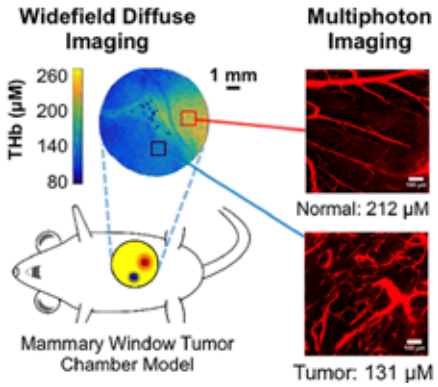
Publication:

Ulaner GA, Hyman DM, Ross DA, et al. 2016. Detection of HER2-positive metastases in patients with HER2-negative primary breast cancer using 89Zr-trastuzumab PET/CT. *J Nucl Med,* 57:1523-1528

The Flare Behind Tumor Imaging to Rapidly Measure Breast Cancer Response to Therapy

Darren Roblyer, Ph.D., Boston University, FY14 Era of Hope Scholar Award

Several imaging procedures are available to monitor breast tumor growth and metastasis; however, none of them measure immediate tumor response to treatments. Dr. Roblyer and his team want to improve upon current imaging capabilities to rapidly detect tumor response to therapies, which will simultaneously prevent exposure to ineffective cytotoxic therapies for the patient. Dr. Roblyer and his team showed improved imaging capabilities of spatial frequency domain imaging (SFDI), a new technique they are using to quantify optical properties of tumors in mice. SFDI will be used in combination with multiphoton microscopy to investigate the possibility of scheduling delivery of multiple drug therapies in mouse models with the goal of enhancing the efficacy of each drug by measuring the immediate tumor response. The findings will then be translated to human breast cancer patients using digital diffuse optical imaging and a wearable infusion monitor. The infusion monitor is capable of detecting an increase in oxyhemoglobin, or the oxyhemoglobin flare, within the first 24 hours of treatment, which is indicative of tumor response to therapy. This toolset developed by Dr. Roblyer and his team may enable clinicians to more quickly identify better treatment options by providing optical signatures of tumor response or resistance to treatment.



Multiscale imaging of mammary tumors. SFDI is used to measure widefield concentrations of hemoglobin, and multiphoton microcopy is used to quantify the morphology of tumor microvasculature. This combination of imaging modalities simultaneously provides micro-scale and widefield (clinically translatable) indications of chemotherapy response and resistance.

Publications:

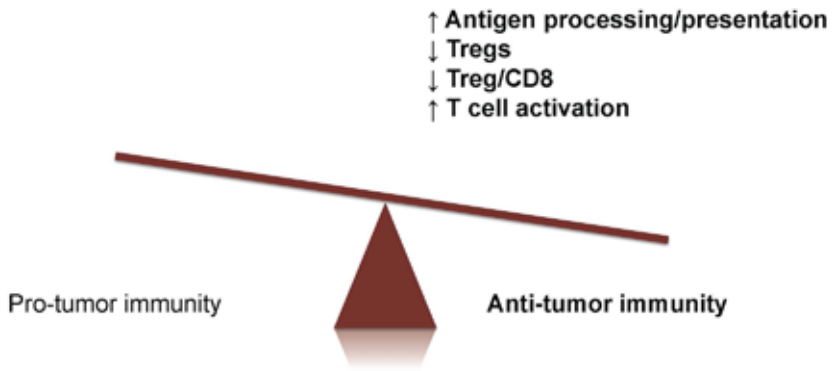
Applegate M and Roblyer D. 2017. High-speed spatial frequency domain imaging (SFDI) with temporally modulated light. *Journal of Biomedical Optics*, 22(7):076019.

Torjesen A, Istfan R, and Roblyer D. 2017. Ultrafast wavelength multiplexed broad bandwidth digital diffuse optical spectroscopy for in vivo extraction of tissue optical properties. *Journal of Biomedical Optics*, 22(3):036009.

CDK4/6 Inhibition Triggers Antitumor Immunity

Sandra McAllister, Ph.D., Brigham and Women's Hospital, FY13 Era of Hope Scholar Award

Dr. Sandra McAllister and colleagues discovered a novel antitumor immunity-promoting function for CDK4/6 inhibitors. Using a mouse model of HER2-positive breast cancer (MMTV-rtTA/tetO-HER2), Dr. McAllister and colleagues observed a 40% reduction in tumor volume after 12 days of abemaciclib treatment. Gene expression analysis of these treated tumors showed that genes related to cell cycle and mitosis were downregulated, while a concomitant increase in genes responsible for promoting antitumor immunity was observed. Intratumoral immune cell analysis revealed a significant reduction in Tregs in abemaciclib-treated MMTV-rtTA/tetO-HER2 tumors, and the ratio of Tregs to cytotoxic T-cells was significantly decreased in the treated tumors. Combining treatment of abemaciclib with an immune checkpoint inhibitor (anti-PD-L1 antibody), Dr. McAllister showed a 70% reduction in tumor volume by day 13. Moreover, growth remained suppressed through day 35, whereas tumors treated with abemaciclib alone resumed growth by day 21. Results from this study support future immunotherapy studies assessing the combination of CDK4/6 inhibitors with other T-cell-directed agents.



CDK4/6 inhibitors shift the balance within breast cancer tissue in favor of anti-cancer immunity.

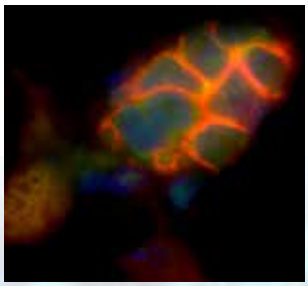
Publication:

Goel S, DeCristo MJ, Watt AC, et al. 2017. CDK4/6 inhibition triggers anti-tumor immunity. *Nature,* 548(7668):471-475

Microenvironments and Signaling Pathways Regulating Early Dissemination, Dormancy, and Metastasis

Julio A. Aguirre-Ghiso, Ph.D., Mount Sinai School of Medicine, FY13 Breakthrough Award

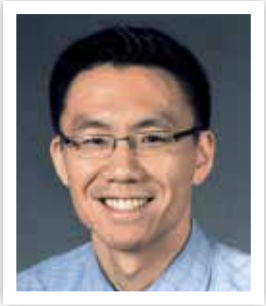
Dr. Aguirre-Ghiso and his team at Mount Sinai School of Medicine uncovered a mechanism of early dissemination and metastasis in human epidermal growth factor receptor 2 (HER2)+ breast cancer. The finding that a subpopulation of early cancer cells can disseminate and metastasize changes the current paradigm of oncogene-driven dissemination prior to proliferation. They found that, while p38+ cells typically retain E-cadherin expression and membrane-localized β-catenin indicative of a non-invasive phenotype, HER2+ cells display a loss of E-cadherin and β-catenin junctions, as well as low levels of phosphorylated ATF2, which are indicators of an invasive cell phenotype that tends to persist in large primary tumors. Furthermore, the team discovered that HER2+ cells from early primary lesions rely on Wnt canonical and non-canonical signaling to induce a phenotype associated with the upregulation of the pro-metastatic transcription factor, TWIST1. Notably, HER2+ DCCs that are detected during the stages of primary tumor growth display a downregulation of the TWIST1 gene, while most HER2+ early DCCs are quiescent and upregulate TWIST1, indicating a dormant phenotype preceding metastatic capacity for the early DCCs. The early DCCs were also found to display a greater ability to intravasate and lodge in secondary organs. These studies warrant further investigation to determine whether changes in TWIST1 and E-cadherin expression control the reactivation of a cancer in a secondary site, such as the lungs.



HER2+ and TWIST+ early disseminated cancer cell precursors in the mammary tissue.

Publication:

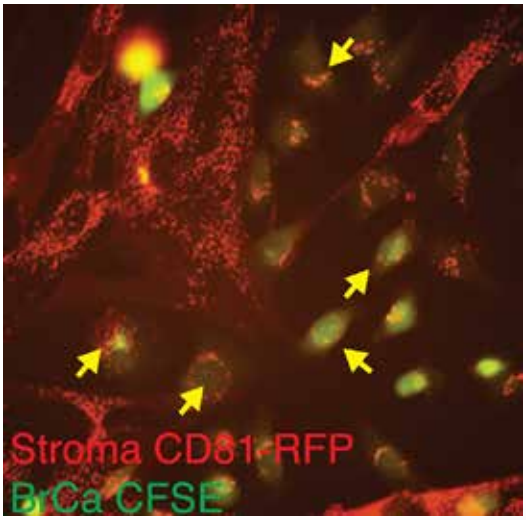
Harper KL, Sosa MS, Entenberg D, et al. 2016. Mechanism of early dissemination and metastasis in HER2+ mammary cancer. *Nature*, 540:588-592.



Uncovering a New Pathway to Target and Treat Breast Cancer Metastasis

Andy Minn, M.D., Ph.D., University of Pennsylvania, FY08 Era of Hope Scholar Award and FY13 Breakthrough Award

Dr. Andy Minn has dedicated his career to challenging the notion that metastatic breast cancer is incurable by studying the interaction between stroma and breast cancer to elucidate pathways that mediate treatment resistance. Using cell culture methods in which interferon-stimulating gene (ISG)-expressing cancer cells were grown with stromal cells (co-culture), the research team discovered that stromal cells released and transferred exosomes to the cancer cells. These exosomes were found to contain an abundance of non-coding ribonucleic acid (RNA). Dr. Minn's group identified that a non-coding RNA called RN7SL1 was responsible for the ability of stromal-derived exosomes to mimic viruses, activate cytoplasmic RNA receptors in breast cancer cells, and induce ISGs. This signaling cascade promotes tumor growth, metastasis, and treatment resistance. Targeted therapies that block key parts of this signaling cascade markedly improve response to therapy in animal models of breast cancer. Dr. Minn and his team also co-cultured TNBC cells with a panel of stromal cells isolated from patients' breast tumors following surgical resection. Results from genetic analyses confirmed that patient's stromal cells were able to activate pro-tumorigenic and ISG signaling pathways within the breast cancer cells. Moreover, harvesting exosomes from the serum of breast cancer patients demonstrated high levels of RN7SL1 in patients with triple-negative tumors. Results from this study elucidate a novel mechanism of "virus mimicry," by which stromal-tumor cell interactions promote an anti-viral response in breast cancer cells; rendering them more aggressive and resistant to treatment. The expression of RN7SL1 in stromal-derived exosomes could serve as a potential biomarker from liquid biopsies to predict whether a patient will respond to chemotherapy or radiation treatments. In conjunction with RN7SL1, the presence of ISGs in primary breast tumors could also be used to further predict how a patient will respond to treatment.



Publications:

Boelens MC, Wu TJ, Nabet BY, et al. 2014. Exosome transfer from stromal to breast cancer cells regulates therapy resistance pathways. *Cell,* 159:499-413.

Nabet BY, Qiu Y, Shabason JE, et al. 2017. Exosome RNA unshielding couples stromal activation to pattern recognition receptor signaling in cancer. *Cell,* 170:352-366.

In the Clinical Pipeline

The BCRP has invested in the discovery and development of multiple therapies and diagnostic tools, many of which have continued to advance through the clinical pipeline. The BCRP is also currently funding several projects with clinical trials that have been initiated or are in preparation.

BCRP-funded *Current phase supported by other sources* *Prior phase supported by other sources*

VACCINES AND IMMUNOTHERAPIES			
NeuVax™ — *Constantin Ioannides and Elizabeth Mittendorf*	**Pre-IND***	**Phase I/II**	**Phase III**
The E75 peptide, an immunodominant HER2 peptide, combined with GM-CSF, has been developed into an immunogenic peptide-based vaccine under the commercial name of NeuVax™ (Galena Biopharma). The vaccine reportedly is effective in 50-60% of HER2+ patients and is now in Phase III clinical trials to evaluate the effectiveness of the vaccine in preventing or delaying breast cancer recurrence after standard of care therapy. In addition, a Phase II clinical trial testing NeuVax™ and trastuzumab in high-risk HER2+ breast cancer patients has started.			
HER2 Peptide-Based Vaccine — *Mary (Nora) L. Disis*		**Phase I/II**	
A HER2 intercellular domain peptide-based vaccine, designed to treat breast cancer by stimulating the immune destruction of remaining cancer cells after primary cancer therapy, showed improved survival in patients with advanced-stage HER2+ breast cancer when administered early in the course of treatment during a Phase II clinical trial in Stage III and IV HER2+ patients. The vaccine has been licensed by EpiThany for further investigation.			
STEMVAC — *Mary (Nora) L. Disis*	**Pre-IND**	**Phase I/II**	
STEMVAC is a multi-antigen vaccine comprised of Th1 epitopes derived from five breast cancer stem cell/EMT immunogenic proteins. It has been shown to be safe and to inhibit tumor growth in mouse models of breast cancer. A Phase I clinical trial is nearing completion in patients with HER2-negative, advanced stage breast cancer to test toxicity and how the vaccine impacts development of immunologic memory. If proven safe, future testing in the prevention setting can be developed.			
Mammoglobin cDNA Vaccine — *William Gillanders*	**Pre-IND**	**Phase I/II**	
Mammoglobin-A, a member of the secretoglobin superfamily, is a novel breast cancer-associated antigen and an exceptional target for breast cancer vaccine therapy. A Phase I clinical trial of a mammoglobin-A cDNA vaccine has been completed and has shown that the vaccine is safe, able to induce specific IFN-γ-secreting CD8 T-cells, and results in longer progression-free survival for patients. A Phase Ib trial of the mammoglobin-A cDNA vaccine in patients receiving neoadjuvant endocrine therapy is underway.			
Folate Receptor Alpha Vaccines — *Keith Knutson and Edith Perez*	**Pre-IND**	**Phase I/II**	
A Phase II clinical trial is being conducted to determine whether a folate receptor alpha vaccine can prevent or delay disease recurrence in patients with TNBC, as this particular receptor has been shown to be highly expressed in TNBC. A safety profile and markers of disease protection will also be determined from this trial. A previous Phase I trial has already demonstrated the safety and immunogenicity of the vaccine.			
HER2 Bi-Armed Activated T-Cells — *Lawrence G. Lum*	**Pre-IND**	**Phase I/II**	
Preclinical studies on HER2 bi-armed activated T-cells showed they induced the development of "memory" antigen-specific cytotoxic T-cells directed at HER2, which led to a Phase I clinical trial in women with HER2+ metastatic breast cancer. Trial results indicated safety and long-term antitumor responses and a Phase II trial is ongoing.			
TRC105 — *Ben Seon*	**Pre-IND**	**Phase I/II**	
TRC105 is a monoclonal antibody that targets endoglin, inhibits angiogenesis, and was found in preclinical models to suppress the growth of both established tumors and new tumors. The antibody is currently in a Phase I/II clinical trial in combination with letrozole and everolimus in breast cancer patients. Several early phase clinical trials are also being conducted in other cancers.			
Mesothelin-Targeted T-Cell Therapy for Metastatic Breast Cancer — *Michel Sadelain and Shanu Modi*	**Pre-IND**	**Phase I/II**	
Preclinical work demonstrated that mesothelin (MSLN) was expressed in 36% of TNBC patients and those MSLN-positive TNBC patients had an increased frequency and interval to develop distant metastases, resulting in a significantly lower overall and disease-specific survival. A Phase I clinical trial is currently being conducted to systemically administer MSLN-targeted chimeric antigen receptor (CAR) T-cells in patients with therapy-refractory, metastatic TNBC, and to compare immune responses between patients who received MSLN CAR T-cells intravenously or intrapleurally.			
AVX901 HER2 Vaccine — *H. Kim Lyerly*	**Pre-IND**	**Phase I/II**	
The VRP-HER2, or AVX901, vaccine is composed of adenoviral and alphaviral vectors expressing the human HER2 gene. A Phase I clinical trial has completed recruitment and treatment, and data analysis is currently ongoing.			

*Investigational New Drug (IND) application

BCRP-funded | Current phase supported by other sources | Prior phase supported by other sources

VACCINES AND IMMUNOTHERAPIES (cont.)

P10s-PADRE — *Thomas Kieber-Emmons* — Pre-IND | Phase I/II

The carbohydrate mimetic peptide vaccine, P10s-PADRE, which targets tumor-associated carbohydrate antigens, was found to be safe, tolerable, and immunogenic in a Phase I clinical trial. In addition, this vaccine demonstrated significant clinical benefit in one subject. Phase II clinical trials in breast cancer, as well as other cancers, have been initiated and are funded by another source.

Combination Vaccine for HER2+ Metastatic Breast Cancer — *Leisha Emens* — Pre-IND | Phase I/II

Parallel mechanistic studies and a Phase I clinical trial testing the combination of trastuzumab, cyclophosphamide, and an allogeneic GM-CSF-secreting breast tumor vaccine for HER2+ metastatic breast cancer. The treatment was found to be safe, tolerable, and immunogenic, and to have clinical benefit. A Phase II clinical trial has been completed, and the results are being analyzed.

Alpha-Lactalbumin Vaccine for Triple-Negative Breast Cancer — *Vincent Tuohy and George Budd* — Pre-IND | Phase I/II

A Phase Ia clinical trial will be conducted to determine the safety and dosage of an alpha-lactalbumin vaccine in TNBC patients that have recovered from current standard-of-care therapy before a Phase Ib clinical trial is conducted to evaluate the safety of the alpha-lactalbumin vaccine in healthy subjects for use in a prophylactic setting.

Engineered T-Cells to Treat Locally Advanced or Metastatic Triple Negative Breast Cancer — *Rongfu Wang and Jenny Chang* — Pre-IND | Phase I/II

A Phase I clinical trial is planned to evaluate the safety and efficacy of using T-cell receptors engineered to recognize the NY-ESO-1 cancer antigen (NY-ESO-1 TCR-transduced T-cells) for the treatment of TNBC. Mechanistic studies are also ongoing to elucidate key chemokines and receptors that enhance T-cell trafficking to tumor sites.

HER2-Specific Helper T-Cell Epitope Vaccine — *Keith Knutson and Amy Degnim* — Pre-IND | Phase I/II

A Phase I clinical trial will be conducted to assess the safety and tolerability of a HER2 subdominant epitope-based vaccine that will enhance HER2-specific CD4 T-cell immunity.

Enhancing the Anti-HER2 CD4 Th1 Response to Prevent Recurrence — *Brian Czerniecki* — Pre-IND | Phase I/II

Phase I clinical trials will be conducted to test whether the combination of a multivalent Th1 epitope anti-oncodriver DNA vaccine and a HER2-pulsed IL-12 secreting dendritic cell (DC1) vaccine can improve complete pathologic response rates in HER2+ breast cancer and prevent recurrence.

NOVEL TECHNIQUES IN TREATMENT

Targeted HER2 Radiotracer — *Gary Ulaner* — Pre-IND | Phase I/II

Growing evidence suggests that HER2 expression may change between primary HER2- lesions and HER2+ metastases, an example of tumor heterogeneity. A Phase I trial is currently underway using a targeted HER2 radiotracer (89Zr-trastuzumab) to determine the proportion of patients with HER2-negative primary breast cancer who develop imagable HER2-positive metastases (NCT 02065609). This trial will also determine whether HER2-targeted therapy results in a measurable treatment response.

Polycationic Peptides for Fluoresence-Guided Surgery — *Roger Tsien* — Pre-IND | Phase I/II

AVB-620, a protease-activatable flourescent peptide, is administered intravenously to patients prior to surgery. A camera system is used to perform fluorescence imaging, which enables surgeons to identify critical cancer margins for tumor resection and examine lymph nodes for invasive disease. AVB-620 has been licensed by Avelas Biosciences, and a Phase Ib clinical trial in breast cancer has been completed (NCT02391194). A Phase II clinical trial studying AVB-620 in women with primary, nonrecurrent breast cancer undergoing surgery recently began in 2017 (NCT03113825).

THERAPEUTICS

Fatty Acid Synthase Inhibitor — *Ruth Lupu and Tufia Haddad* — Pre-IND | Phase I/II

A Phase II clinical trial recently started to recruit patients to evaluate the efficacy of the fatty acid synthase inhibitor, TVB-2640 (3-V Biosciences), in combination with paclitaxel and trastuzumab in patients with taxane-resistant metastatic HER2+ breast cancer (NCT 03179904).

Center of Excellence for the Eradication of Brain Metastasis — *Patricia Steeg* — Pre-IND | Phase I/II

An FY05 BCRP Center of Excellence Award formed the first group to examine brain metastasis in a comprehensive multidisciplinary manner. A Phase I/II clinical trial based on the group's preclinical findings using temozolomide has been initiated (NCT03190967). The study involves treating patients with HER2+ breast cancer with T-DM1, either alone or combined with temozolomide, to see if the combination will prevent formation of new metastases in the brain.

Pembrolizumab and Tremelimumab for Treatment of Oligometastasis — *Andy Minn* — Pre-IND | Phase I/II

Dr. Minn and colleagues have opened a Phase I clinical trial, with assistance from Merck, that examines radiation to a metastatic lesion in combination with the immune checkpoint inhibitor pembrolizumab (PD-1 inhibitor) for patients with metastatic cancers for which anti-PD-1 therapy has failed, or for patients who have completed at least one regimen of systemic therapy (https://clinicaltrials.gov/ct2/show/NCT02303990). A second Phase I trial has also started to test radiation in combination with dual immune checkpoint blockade, using tremelimumab (anti-CTLA-4) and MED14736 (anti-PDL1) for patients with metastatic breast cancer and other cancers (https://clinicaltrials.gov/ct2/show/NCT02639026).

Combining Aromatase and Src Inhibitors — *Joyce Slingerland and Isabel Chu* — Pre-IND | Phase I/II

BCRP-funded studies found that a two-pronged approach to therapy that includes both antiestrogens and drugs that preserve p27 may be effective in arresting cell cycle progression in breast cancer. Phase I and II trials have begun, which will test the tolerability and efficacy of anastrozole, an aromatase inhibitor that stops estrogen production, together with Src inhibitor AZD0530, in post-menopausal women with ER+ breast cancer.

5-Fluoro-2'deoxycytidine (FdCyd) — *Edward Newman* — Pre-IND | Phase I/II

Preclinical studies demonstrated the effects of FdCyd with tetrahydrouridine on the reversal of DNA methylation in several genes expressed by breast cancer cells. A BCRP-funded Phase I trial has been completed, and an NCI supported Phase II trial has been initiated.

Anti-Androgen Therapy (Enzalutamide) — *Anthony Elias and Jennifer Richer* — Pre-IND | Phase I/II

Higher levels of androgen receptors were found to be expressed on ER+ breast cancers that are resistant to anti-estrogen therapy. These cells were also shown to proliferate in response to androgen, which was inhibited by enzalutamide. Phase I and II clinical trials are currently testing the safety and efficacy of enzalutamide in breast cancer patients, in combination with other standard treatments.

Meclofenamate for Brain Metastasis — *Joan Massague* — Pre-IND | Phase I/II

The BCRP funded work that created the first mouse models of latent metastasis of breast cancer. This work identified a carcinoma-astrocyte gap junction as a mechanism for metastatic outgrowth that can be inhibited by gap junction modulators such as Meclofenamate, a Food and Drug Administration (FDA)-approved non-aspirin non-steroidal anti-inflammatory drug. As a result, a Phase I clinical trial of Meclofenamate is currently enrolling patients with recurrent or progressive brain metastasis from a solid primary tumor (NCT 02429570).

Aspirin as Adjuvant Therapy for Node-Positive Breast Cancer — *Eric Winer and Michelle Holmes* — Pre-IND | Phase I/II | Phase III

Epidemiological and preclinical data suggest aspirin may reduce breast cancer recurrence and improve survival. A Phase III randomized, placebo-controlled trial of aspirin among breast cancer patients with node-positive disease recently began (NCT 02927249). Using invasive disease-free survival as the primary end point, the trial will assess adherence to and toxicity of long-term aspirin use, as well as create a longitudinal biospecimen and epidemiologic data repository.

Molecular Triage Approach for a More Effective and Less Toxic Therapy for HER2+ Breast Cancer — *Mothaffar Rimawi and Rachel Schiff* — Pre-IND | Phase I/II

The goal of this study is to develop a Phase II clinical trial using a molecular classifier to identify patients who can benefit from anti-HER2 therapy without added chemotherapy. The molecular classifier is currently being confirmed, which will lead to validation of the genomic alterations associated with resistance.

A Novel Druggable Pathway that Promotes Bone Loss in Breast Cancer Patients — *Alana Welm* — Pre-IND | Phase I/II

Plasma samples from a Phase I clinical trial (NCT01721148) using the RON kinase inhibitor, BMS-777607/ASLAN002, in metastatic cancer patients showed that a majority of patients had decreased levels of an osteolysis biomarker and increased levels of a marker indicative of bone repair after treatment with the RON kinase inhibitor.

BCRP-funded | Current phase supported by other sources | Prior phase supported by other sources

THERAPEUTICS (cont.)

T-DM1 — *Dennis Slamon* — Pre-IND | Phase I/II | Phase III

Based on results obtained from BCRP-funded preclinical studies, a Phase III study (KRISTINE, Hoffmann-La Roche, NCT02131064) was conducted to evaluate the efficacy and safety of trastuzumab emtansine plus pertuzumab compared with chemotherapy plus trastuzumab and pertuzumab for HER2+ breast cancer.

Talazaparib — *Dennis Slamon* — Pre-IND | Phase I/II

Preclinical studies support the use of the novel PARP inhibitor, talazoparib, in non-BRCA mutant triple-negative disease and other luminal subtypes of breast cancer. Phase Ib clinical studies have been initiated to evaluate the safety of talazaparib in combination with other breast cancer therapeutics.

DIAGNOSTICS

Intraductal Techniques — *Susan Love* — Pre-IND

An endoscope was modified to enter and examine milk ducts through their openings at the nipple. This laid the groundwork for the development of sophisticated and miniaturized endoscopes that enable the retrieval of cell samples for detailed study of the breast ducts, which are believed to be the site where most breast tumors initiate.

Skp2 Oncogene — *Michele Pagano* — Pre-IND | Phase I/II | Phase III

High Skp2 expression correlating with destabilization of p27 is associated with poor prognosis in breast cancer patients. These findings contributed to the use of Skp2/p27 immunohistochemical analysis as a prognostic test performed in clinical pathology laboratories. Skp2 is currently being assessed as an in vivo diagnostic test for breast cancer.

Products Making an Impact

THERAPEUTICS

Trastuzumab (Herceptin®)

Dennis Slamon

Herceptin® (trastuzumab) is a monoclonal antibody that targets the 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.

ATLAS Clinical Trial

Richard Peto

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 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 those who took it for 5 years. These findings changed clinical practice.

Prone Radiotherapy

Silvia Formenti

Clinical trials were conducted 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 DCIS. Patients were treated in the prone position, greatly reducing unnecessary radiation exposure of the heart and lungs. Current clinical trials and long-term follow-up will continue to examine the prone radiotherapy approach for efficacy and toxicity.

Palbociclib (Ibrance®)

Dennis Slamon

BCRP-supported preclinical work on the CDK inhibitor palbociclib (Ibrance®) led to Pfizer support for Phase I and II trials combining Ibrance® with letrozole. Results showed an increase in median progression-free survival, prompting "Breakthrough Therapy" status by the FDA and Pfizer's initiation of a Phase III clinical trial. In 2015, FDA grants accelerated approval of Ibrance® with letrozole for the treatment of ER+/HER2+ breast cancer in post-menopausal women.

Ribociclib (Kisqali®)

Dennis Slamon

Ribociclib (Novartis) in combination with an aromatase inhibitor was approved by the FDA in March 2017 for the treatment of women with ER+/HER2- metastatic breast cancer based on results from BCRP-funded preclinical studies.

Abemaciclib (Verzenio™)

Dennis Slamon

Abemaciclib (Eli Lilly) was approved by the FDA in September 2017 for the treatment of women with HR+, HER2- advanced or metastatic breast cancer. Abemaciclib can be taken as a monotherapy or in combination with fulvestrant.

DIAGNOSTICS

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 both tumor staging and whether 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.

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. MBI is an FDA-approved, commercially available technology.

Digital Mammography and Breast Tomosynthesis

Laurie Fajardo and Daniel Kopans

Digital mammography allows for an expanded detection range of x-ray signals compared to standard film mammography. The BCRP provided support to optimize this 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.

Products Making an Impact

MetaSite Breast™

John Condeelis and Allison Harney

Tumor Microenvironment of Metastasis (TMEM) sites are composed of a stable interaction between three specific cells: an endothelial cell, a tumor-associated macrophage, and a MenaCalc-positive tumor cell (expressing high levels of the MenaINV protein isoform and low levels of the Mena11a isoform). In work funded by the BCRP, Drs. Condeelis and Harney found that TMEM sites are the only doorway for tumor cell entry into blood vessels. In other studies, TMEM were found in all primary and secondary sites and in all stages of breast cancer progression, making TMEM the common dissemination marker in all breast tumors and their associated distant sites. In collaboration with MetaStat, Inc., Dr. Condeelis and colleagues clinically validated the MetaSite Breast™ test, which measures TMEM levels to predict the metastatic potential of the primary tumor. MetaSite Breast™ has been licensed to MetaStat, Inc., and is Clinical Laboratory Improvement Amendments– certified and publically available.

MenaCalc™

John Condeelis and Jeanine Pignatelli

Breast cancer cells enter the bloodstream at sites called TMEM and spread elsewhere in the body. TMEM sites are correlated with low levels of Mena11a (MenaCalc™). A prospective clinical trial supported by the BCRP demonstrated that the MenaCalc™ score in fine needle biopsies predicted the TMEM score (i.e., a high number of TMEM sites) in resected primary breast tumor tissue. In addition, two retrospective trials showed that the MenaCalc™ score can be used as a prognostic marker for distant recurrence. MenaCalc™ has been licensed to MetaStat, Inc., and has been clinically validated for use in breast cancer treatment decision making. It has also been used for other types of cancers, including early-stage non-small cell lung carcinoma, as an independent prognostic factor and predictor of metastasis.

PATIENT RESOURCES AND REGISTRIES

BreastCancerTrials.org

Laura Esserman

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. BCRP funding contributed to the development of an online resource (BreastCancerTrials.org) that educates patients about breast cancer clinical trials and matches them with appropriate trials.

Carolina Mammography Registry

Bonnie Yankaskas

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. The registry became a member site of the NCI Breast Cancer Surveillance Consortium, a national registry that provides a resource for researchers to study mammography screening on a national level.

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.

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 web site, which is available in English and Spanish, includes updates on current research, treatments, and clinical trials, as well as personal experiences written by patients.

RISK ASSESSMENT

BRCA2 617delT Mutation

David Goldgar and Susan Neuhausen

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.

OncoVue®

Eldon Jupe

Risk association studies funded by the BCRP formed the foundation for a breast cancer risk assessment test. 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 her 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 more than 30 breast care centers in the United States.

PTEN

Michael Wigler

BCRP funding contributed to the original discovery of the PTEN (phosphatase and ten- sin 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.

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 two-fold 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.

BROCA Cancer Risk Panel

Tomas Walsh and Mary-Claire King

An estimated 70% of families with multiple cases of breast cancers have no known gene mutations that increase their risk to the disease. Dr. Walsh, in collaboration with Dr. King, identified and validated rare mutations, termed copy-number variants, which led to development of a comprehensive test named “BROCA” that enables assessment of all known breast cancer genes and all mutation types in a single assay. The BROCA test is currently available through the University of Washington by physician request.

PROGNOSTICS

Breast Cancer Index

Dennis Sgroi

Women with ER+ breast cancer have an increased risk of relapse many years after their initial diagnosis. To identify women with an increased risk of disease recurrence, Dr. Sgroi validated biomarkers that correlated with relapse-free survival and tumor grade, leading to a risk assessment test termed the Breast Cancer Index (BCI). The BCI test, which is now commercially available through bioTheranostics, provides a quantitative assessment of the likelihood of early and late recurrence, as well as extended endocrine therapy.

RESEARCH RESOURCES

Expression Arrest™ shRNA Libraries

Gregory Hannon and Stephen Elledge

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.

Three-Dimensional Culture Systems

Mina Bissell

The BCRP supported the development of 3-D culture systems that have made important contributions to 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.

Novel Models for Breast Tumor Growth and Metastasis

Alana Welm

Orthotopic breast tumor models can replicate the diversity of human breast cancer through patient-centric models for tumor growth, metastasis, drug efficacy, and prognosis. These models exceed the current standard of cell line xenograft models. Funding from the BCRP has supported generation of publicly available tumor graft mouse models. Since some of the most promising therapies affect the immune response and need to be tested in preclinical models before entering trials, work is now underway to develop immunocompetent mouse models representing each subtype of human breast cancer to predict the response to therapy. Researchers interested in obtaining the models should refer to http:// www.ncbi.nlm.nih.gov/pubmed/22019887. Additional unpublished models are also available by contacting Dr. Welm.

For more information, please visit
http://cdmrp.army.mil
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