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 $12.0 billion since its inception through fiscal year 2018 (FY18). 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 $3.6 billion in Congressional appropriations through FY19. 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. The outcomes of BCRP-funded research will ultimately benefit military Service members, Veterans, military beneficiaries, and the general public.

FY92–FY17 BCRP Portfolio

- Clinical & Experimental Therapeutics: 24.7%
- Detection & Diagnosis: 11.2%
- Primary Prevention: 1.7%
- Pathobiology: 15.3%
- Immunology: 3.2%
- Endocrinology: 4.0%
- Genetics & Molecular Biology: 10.3%
- Computational Biology: 0.1%
- Research Resources: 6.5%
- Complementary & Alternative Medicines: 0.5%
- Epidemiology: 3.3%
- Biobehavioral Sciences: 1.6%
- Health Care Delivery: 1.2%
BCRP 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–FY17 BCRP Funding Invested by Overarching Challenges

- Prevent breast cancer $26,305,170
- Identify determinants of initiation, risk, or susceptibility $20,078,501
- Distinguish deadly breast cancer $30,933,200
- Conquer overdiagnosis and overtreatment $20,859,796
- Revolutionize treatment regimens $133,051,400
- Identify why metastases occur $43,668,927
- Determine how to prevent lethal recurrence $35,210,820
- Identify what drives breast cancer growth $71,145,720
- Identify why metastases occur $43,668,927
- Prevent breast cancer $26,305,170
- Eliminate metastatic mortality $148,352,430

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 2018, there were over 626,000 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 reduction, avoidance of use of combined estrogen and progestin menopausal hormones, reduced alcohol consumption and smoking, and increased physical activity, are weakly to moderately associated with breast cancer risk.
- 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.


RELEVANCE TO MILITARY HEALTH

Breast cancer is the most common non-skin cancer in women, causing the most cancer-related deaths in women under the age of 401. Female active duty Service members have a 20-40% higher incidence rate of breast cancer than the general public2. The incident rate of breast cancer for active duty women is seven times higher than the average incident rate of fifteen other cancer types across all Service members3. The outcomes of BCRP-funded research will ultimately benefit military Service members, Veterans, military beneficiaries, and the general public.

1 www.cdc.gov/cancer/dataviz
“The DoD BCRP has a unique, flexible structure that enables it to fund innovative, high-risk, high-return research that focuses on the continued challenges of breast cancer. The program is able to quickly respond to current scientific advances; it is efficient, and is accountable to the public and is transparent. The program has produced exceptional results through the integrated efforts of the many partners involved in the program. The DoD BCRP continues to challenge the status quo and to encourage new ideas, breakthroughs, and collaboration – all with a sense of urgency. It is an honor to serve, along with other committed advocates, scientists, clinicians, and the US Army, as we work together to end breast cancer.”

**Pat Haugen, Consumer Reviewer and FY19 Programmatic Panel Chair**

“Being a grantee and a reviewer of DoD BCRP for the past 7 years, I deeply feel its uniqueness - always aiming to completely eradicate breast cancer and always putting patients as the highest priority. The overarching questions raised by DoD BCRP generated long-standing impact and significantly altered the landscape of breast cancer research toward more direct, immediate, and effective treatments. At a personal level, the support from DoD BCRP not only allowed me to perform cutting-edge research, but also provided a platform to work with patient advocates. Their passion and inspiration have been transformative to my career.”

**Xiang Zhang, Ph.D., Baylor College of Medicine**

“Metastatic breast cancer is the only cancer that kills, and research is the only effort that truly helps patients do what we want to do - LIVE! That’s why I applied to be a patient advocate reviewer with the DoD BCRP. This program has played an important funding role for some of the most meaningful breast cancer discoveries in history. And I got to be part and have a say about what should be coming next. It was one of the most rewarding experiences in my advocacy career.”

**Julia Maues, Consumer Reviewer**

“When consumers sit with scientists at the table, it’s not about that consumer’s breast cancer; it’s about the breast cancer to be diagnosed in generations yet to come. I’m feeling the sense of urgency inside of myself. I do not want my granddaughters to be diagnosed with breast cancer. I want them to have a screening tool that is so much better than a mammogram, and I want the potential outcomes to be so much better in their life for them then they are for us today. It’s not about me. My life is what it is. It’s about theirs. So my sense of urgency feeds into my commitment to the Department of Defense Breast Cancer Research Program. At least with this program, I believe we will get the answers.” (Marlene died of metastatic breast cancer on July 17, 2018.)

**Marlene McCarthy, Consumer Reviewer**
Atf3 in Non-Cancer Host Cells is Linked to Chemotherapy-Enhanced Metastasis in Breast Cancer

Tsonwin Hai, Ph.D., Ohio State University, FY13 Breakthrough Award – Funding Level 2

Chemotherapeutic agents, such as paclitaxel (PTX), induce changes within both the tumor and host microenvironments and are thought to contribute to increased chemoresistance and cancer progression. Dr. Hai and her research team have shown that increased breast cancer metastasis after treatment with PTX is dependent on a stress-inducible gene, activating transcription factor 3 (Atf3), in non-cancerous host cells. In addition, they showed that chemotherapy—a stress signal—induces Atf3 and alters immune responses that not only promote more cancer cells (the “seeds”) to escape from the primary tumors, but also change the distant tissues (the “soil”) to be more hospitable to cancer cells. The net result is that chemotherapy, despite reducing primary tumor size, paradoxically increases metastasis. Dr. Hai and her research team also used Oncomine, a publicly available genome-wide expression search engine, to test the relevance of their observations in human samples. Mining a patient database indicated that breast cancer patients who had undergone neoadjuvant chemotherapy treatment had increased expression of ATFR3 in breast tumor stroma. Additionally, similar to what was observed in mice, breast cancer patients with metastatic disease and ATF3 expression in tumor stroma also had increased expression of genes shown to create an immunosuppressive microenvironment that is more hospitable to cancer cells. These results suggest that targeting the effects of host cell ATFR3 could help counteract the pro-metastatic effects of chemotherapy for breast cancer patients.

Publication:

References:

A model depicting how host-Atf3 and PTX affect steps in the metastatic cascade. (Figure modified from Chang et al. 2017. PNAS 114:E7159-E7168)

A Combination Treatment Strategy for Paclitaxel-Resistant Triple-Negative Breast Cancer

David H. Gorski, M.D., Ph.D., Wayne State University School of Medicine, Barbara Ann Karmanos Cancer Institute, FY14 Breakthrough Award – Funding Level 1

Among those diagnosed with breast cancer, approximately 10%-20% will be diagnosed with triple-negative breast cancer (TNBC), an aggressive subtype of breast cancer that currently lacks targeted treatment options and often recurs. The current standard of care for TNBC includes surgery, radiation, and chemotherapy agents that can lead to toxic side effects for patients. In order to reduce toxicities associated with the current standard of care and improve treatment efficacy, Dr. Gorski combined riluzole, an orally available drug that has been approved by the U.S. Food and Drug Administration (FDA) to treat amyotrophic lateral sclerosis, with PTX. Results from the study showed that the combination treatment of riluzole and PTX resulted in greater inhibition of TNBC cell growth, with a concomitant increase in TNBC cell death than when PTX was used alone. The greatest sensitivity to the combination treatment was observed in PTX-resistant tumors, suggesting PTX resistance could be reversed with riluzole. In preclinical TNBC mouse models, Dr. Gorski showed that TNBC tumors treated with the combination treatment regimen had a drastically reduced growth rate compared to tumors treated with each drug separately. Taken together, these data support that riluzole and PTX act synergistically to inhibit the growth of TNBC cells while also promoting TNBC cell death.

Publication:
Imaging Agent, Fluorodeoxyglucose (18F-FDG), Transforms Chemotherapeutics into Phototherapy for Precise Treatment of Metastatic Breast Cancer
Samuel Achilefu, Ph.D., Washington University School of Medicine, FY15 Distinguished Investigator Award

Phototherapy utilizes light to selectively and spatially activate light-sensitive agents capable of killing tumor cells. Because light does not penetrate into deep tissues, phototherapy has not been a treatment option for bone metastases. Using Cerenkov radiation-induced therapy (CRIT), an alternative approach to phototherapy, Dr. Achilefu delivered and activated a light-sensitive agent to bone metastatic breast cancer cells in mice. Results demonstrated that the Cerenkov radiation emitted by 18F-FDG could be used to activate the light-sensitive chemotherapeutic agent, titanocene (TC), incorporated into human serum albumin (HSA) nanoparticles (HSA-TC) at the site of bone metastatic lesions. A decrease in overall metastatic burden and tumor growth was observed in CRIT-treated mice. In addition, the team showed that HSA-TC specifically honed to areas with a high metastatic burden. Importantly, mice treated with CRIT revealed no adverse bone marrow stem cell toxicity. Bone marrow repopulation experiments demonstrated that there was no significant difference in hematopoietic reconstitution in mice who received either untreated or CRIT-treated bone marrow progenitor stem cells. Taken together, Dr. Achilefu demonstrated that light-sensitive chemotherapeutic agents can be used to target and slow the growth of metastatic lesions, providing a potential new treatment approach for advanced metastatic breast cancer patients.

Publication:

Her2 and TrkB as Dual Therapy Targets for Her2+ Breast Cancer Brain Metastases
Rahul Jandial, M.D., Ph.D., City of Hope, FY14 Breakthrough Award – Funding Level 1

Over one-third of patients diagnosed with human epidermal growth factor receptor-2 positive (Her2+) primary breast tumors will develop metastases in the brain, even when systemic disease at other sites is in remission. Brain-derived neurotrophic factor (BDNF) is a neurotrophin in the brain that can bind to the tropomyosin-related kinase B (TrkB) receptor and activate several pathways within cells. Dr. Jandial showed that astrocyte-derived BDNF in the brain microenvironment facilitates the initiation and growth of Her2+ breast cancer metastases in the brain. Human primary tumor and brain metastatic tissue from patients with Her2+ or TNBC revealed that activated Her2 and TrkB were both higher in the brain metastatic tissue from Her2+ patients compared to the primary tumor and to TNBC brain metastases. In addition, Her2 and TrkB were found to be co-localized in Her2+ breast cancer brain metastases. Dr. Jandial and his team also showed that, when patient-derived Her2+ breast cancer brain metastatic cells were injected into mice, colonization in the brain occurred; blocking of TrkB expression in these cells prevented the formation of significant brain metastases. Moreover, results showed that BDNF promotes the physical interaction of Her2 and TrkB receptors in patient-derived breast cancer brain metastatic cells. Data from Dr. Jandial’s work indicate that TrkB could be a potential therapeutic target for the treatment or prevention of brain metastases in patients with Her2+ breast cancer disease.

Publication:
The Link Between Chromosomal Instability and Metastatic Progression in Triple-Negative Breast Cancer
Samuel Bakhoum, M.D., Ph.D., Memorial Sloan Kettering Cancer Center, FY15 Breakthrough Award – Funding Level 1

Chromosomal instability (CIN) results in an abnormal number or structure of chromosomes within a cell. CIN has been shown to correlate with metastasis and is associated with an increased risk of recurrence and death in breast cancer. While CIN is a hallmark of cancer that has been shown to correlate with metastasis, the mechanistic role of CIN in metastatic progression remains to be elucidated. Dr. Bakhoum and his research team sought to determine the mechanisms by which CIN contributes to metastasis in TNBC. Using cell line models of TNBC in which his research team overexpressed (CIN-low) or under-expressed (CIN-high) proteins responsible for maintaining chromosome integrity during cell division, he showed that errors in chromosome segregation (CIN-high) activate the noncanonical NF-κB (nuclear factor kappa-light-chain-enhancer of activated B-cells) pathway in a cGAS-STING (cyclic GMP-AMP synthase-stimulator of interferon genes)-dependent manner. Activation of noncanonical NF-κB via cGAS-STING signaling in CIN-high TNBC cells caused the cancer cells to transition to a mesenchymal state, indicative of metastatic potential, increase their invasive capabilities, and activate inflammatory pathways, which promoted metastasis. Using a mouse model of TNBC, Dr. Bakhoum and colleagues confirmed that mice injected with CIN-low TNBC cells significantly lowered the cancer cells’ ability to colonize in the bone, lungs, and brain, thus decreasing the overall metastatic burden. Overall survival was also significantly improved in mice harboring CIN-low metastatic breast tumors when compared to CIN-high metastases (207 days compared to 70 days, respectively). Moreover, the researchers identified a 23-gene CIN signature that predicted distant metastasis-free survival in a meta-analysis and validation cohort of patients with breast cancer, independent of tumor subtype, grade, or lymph node status, suggesting the CIN signature could serve as a prognostic tool for clinicians.

Publication:

Therapeutic Antibody Targeting Tumor- and Osteoblastic Niche-Derived Jagged1 Sensitizes Bone Metastasis to Chemotherapy
Yibin Kang, Ph.D., Princeton University, FY12 Collaborative Scholars and Innovators Award

More than 70% of late-stage breast cancer patients suffer from osteolytic bone metastases that are caused by tumor-initiated hyperactivity of bone-resorbing osteoclast cells. Recent reports suggest disseminated tumor cells (DTC) from breast cancers that express the Notch signaling pathway ligand, Jagged1, facilitate a pro-tumor niche in the bone by activating a positive feedback loop where both the resident bone-building osteoblasts and bone-destroying osteoclasts become activated, causing release of tumor cell survival factors from the bone. Dr. Kang and his team sought to exploit the expression of Jagged1 in DTCs and successfully developed a fully humanized monoclonal antibody, 15D11, with high affinity for human Jagged1. Preclinical studies demonstrated that 15D11 was well-tolerated and had low toxicity profiles. Additionally, pre-treatment with 15D11 not only prevented the establishment of bone metastases in mice injected with human breast cancer cells overexpressing Jagged1, but also protected bones from excessive osteoclast-induced osteolysis. Moreover, 15D11 was shown to synergize with the chemotherapeutic agent, PTX, to cause a 100-fold reduction of established bone metastatic lesions in mice harboring Jagged1-expressing tumors. Surprisingly, a reduction in bone metastatic load was also observed when 15D11 was administered in combination with PTX in mice harboring low Jagged1-expressing tumors. Further investigation into why the low Jagged-1 expressing bone metastases responded to combination therapy led the team to discover that chemotherapy induced expression of Jagged1 in osteoblast cells, which in turn provided survival signals to tumor cells and mediated their ability to become resistance to PTX treatment, a phenotype that could be reversed upon administration of 15D11 with PTX. Results from this study suggest that 15D11 could serve as a powerful new therapeutic to both prevent metastatic recurrences to the bone and combat established bone metastases in breast cancer patients.

Publication:
Women who carry mutations within their Breast Cancer 1 (BRCA1) gene have a total lifetime risk of up to 85% for developing breast cancer. Current preventative options for these women are limited to prophylactic mastectomy, an extremely invasive procedure, and/or intensive screening and monitoring, all of which carry detrimental physical and psychosocial side effects. Epidemiological studies have shown that serum levels of receptor activator of nuclear factor κB (RANK) and its ligand (RANKL) are elevated among BRCA1 mutation carriers. Examining the role of RANK/RANKL in BRCA1 mutation-driven breast cancers, Dr. Penninger and his team showed that high RANK and RANKL protein expression could be found in 70.4% and 59.1% of BRCA1 mutation carrier breast cancer tumor samples, respectively. Dr. Penninger demonstrated that inhibiting RANKL with denosumab delayed the onset, lowered the incidence, and attenuated the progression of breast cancer. Results from Dr. Penninger’s BCRP-funded Innovator Award supported the initiation of a randomized, double-blind, placebo-controlled Phase III clinical trial that is aimed at determining whether the preventative effects of denosumab (XGEVA®) are effective in preventing breast cancer in BRCA1 mutation carrier women (https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-002505-35/AT). This multi-center clinical trial is being sponsored by the Austrian Breast and Colorectal Cancer Study Group, with support from Amgen, Ltd., and includes 15 sites across three continents, including the National Cancer Institute (NCI) and Harvard Medical School in the United States. The study aims to recruit 2,918 patients between the ages of 18 and 64 who harbor a mutation in BRCA1 and have not yet been diagnosed with breast cancer. Patients will be randomized and receive either denosumab or placebo, and the time to the development of breast cancer will be evaluated to determine whether denosumab reduces the risk of any breast cancer (invasive or ductal carcinoma in situ [DCIS]) from developing. Should this Phase III clinical study demonstrate that denosumab can reduce the risk of development of breast cancer in BRCA1 mutation carriers, it would be a feasible strategy that could be rapidly incorporated into clinical practice to prevent breast cancer development in BRCA1 mutation carrier patients.

Publications:
Targeting the Cytoskeletal Physics of Circulating Breast Tumor Cells to Reduce Metastasis

Stuart S. Martin, Ph.D., University of Maryland, Baltimore (UMB) Greenebaum Comprehensive Cancer Center, FY10 Era of Hope Scholar Award

Dr. Martin discovered that detached breast cancer cells form a new tubulin-based cancer cell appendage, termed microtentacles, which promote metastasis of circulating tumor cells (CTCs). Using microfluidic cell tethering technologies, Dr. Martin, in collaboration with Dr. Christopher Jewell’s bioengineering group at the University of Maryland, College Park, developed a strategy to capture and study CTCs in a non-adherent microenvironment. The microfluidic cell tethering technology they developed allowed for high-resolution images of the tethered cells to be obtained in real time and allowed the team to develop an automated analysis of microtentacles behavior in response to drug treatment. In addition, Dr. Martin and his team sought to develop a clinical technology capable of isolating live CTCs from patient blood samples. In collaboration with the nanotechnology company Creatv Microtech, Inc., a microfiltration approach called CellSieve™ was developed, which utilizes wafer photolithography to generate precise pore sizes on a membrane. CellSieve™ allows patient blood to rapidly flow through the CellSieve™ filter, efficiently trapping CTCs while allowing red and white blood cells to pass through. CellSieve™ does not require chemical fixation of cells and allows for a more detailed imaging of live CTCs. Moreover, using CellSieve™, Dr. Martin and his team identified a novel circulating cancer-associated macrophage-like cell (CAML) that was found to be present in the blood of cancer patients and could differentiate patients with malignant and benign disease from those without disease as no CAMLs were detected in blood samples from healthy patient controls. The development of new microfluidic cell tethering technology and CTC isolation methods now provides an integrated platform for scientists to both test anti-metastatic therapies and rapidly characterize patient tumor cells for metastatic potential and drug response.

“The DoD BCRP and its Era of Hope Scholar Award have had a formative influence on me and my research. The BCRP’s vision of a world without breast cancer leads to a very different approach for supporting breast cancer research than do other federal funding agencies. This has allowed us to focus deeply on discovering how to target specific types of white blood cells to treat metastatic breast cancer – a goal that I am passionate about. The BCRP has also given me and my lab the unique opportunity to work with consumer advocates. It has been inspirational to discuss our research with the people that will ultimately benefit from our discoveries, and from these discussions have emerged new ideas that are driving our current research projects on preventing metastatic recurrence.”

Mikala Egeblad, Ph.D., Cold Spring Harbor Laboratory

RESEARCH HIGHLIGHTS
CLINICAL PIPELINE
PRODUCTS
**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.

### VACCINES AND IMMUNOTHERAPIES

**NeuVax™ — Constantin Ioannides and Elizabeth Mittendorf**

The E75 peptide, an immunodominant HER2 peptide, combined with granulocyte-macrophage colony-stimulating factor (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 a Phase III clinical trial to evaluate the effectiveness of the vaccine in preventing or delaying breast cancer recurrence after standard of care therapy has been completed (NCT01479244). In addition, a Phase II clinical trial testing NeuVax™ and trastuzumab in high-risk HER2+ breast cancer patients is ongoing (NCT02297698).

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

An 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 III clinical trial in Stage III and IV HER2+ patients (NCT00791037). The vaccine has been licensed by EpiThany for further investigation. A current Phase III trial is using the vaccine to treat patients with stage IV HLA-A2 and HER2+ breast or ovarian cancer receiving trastuzumab (NCT00194714).

**STEMVAC — Mary (Nora) L. Disis**

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 (NCT02157051). If proven safe, future testing in the prevention setting can be developed.

**Mammaglobin cDNA Vaccine — William Gillanders**

Mammaglobin-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 mammaglobin-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 (NCT00807781). A Phase Ib trial of the mammaglobin-A cDNA vaccine in patients receiving neoadjuvant endocrine therapy is underway (NCT02204098).

**Folate Receptor Alpha Vaccines — Keith Knutson and Edith Perez**

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 (NCT02593227). 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**

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 III clinical trial in women with HER2+ metastatic breast cancer (NCT03272334). The Phase I trial results indicated safety and long-term antitumor responses, and the Phase II trial is ongoing.

**TRC105 — Ben Seon**

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 (NCT02520063). 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**

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 among patients who received MSLN CAR T-cells intravenously or intrapleurally (NCT02792214).

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*Investigational New Drug application
### VACCINES AND IMMUNOTHERAPIES (cont.)

#### AVX901 HER2 Vaccine — H. Kim Lyerly

The VRP-HER2, or AVX901, vaccine is composed of an alphaviral vector expressing the human HER2 gene. Preclinical models demonstrated immunogenicity and anti-tumor activity of the vaccine. In a Phase I clinical trial, the vaccine was found to be safe with no dose limiting toxicity when given alone or in conjunction with other HER2-targeting therapies, and provided significant clinical benefit in HER2+ breast cancer patients (NCT01526473). A Phase II trial is planned to evaluate whether pembrolizumab increases the AVX901-mediated tumor infiltrating and peripheral blood immune response in patients with recurrent or metastatic HER2+ breast cancer (NCT03632941).

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#### P10s-PADRE — Thomas Kieber-Emmons

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 (NCT01390064). In addition, this vaccine demonstrated significant clinical benefit in one subject. Phase II clinical trials in breast cancer (NCT02229084), as well as other cancers, have been initiated and are funded by another source. A Phase II trial testing P10s-PADRE with neoadjuvant chemotherapy in TNBC patients is scheduled to begin in 2019 (NCT02938442).

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#### Combination Vaccine for HER2+ Metastatic Breast Cancer — Leisha Emens

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 were conducted. 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 (NCT00399529).

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#### Alpha-Lactalbumin Vaccine for Triple-Negative Breast Cancer — Vincent Tuohy and George Budd

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.

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#### Engineered T-Cells to Treat Locally Advanced or Metastatic Triple Negative Breast Cancer — Rongfu Wang and Jenny Chang

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.

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#### HER2-Specific Helper T-Cell Epitope Vaccine — Keith Knutson and Amy Degnim

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.

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#### Enhancing the Anti-HER2 CD4 Th1 Response to Prevent Recurrence — Brian Czerniecki

A Phase I clinical trial has been initiated and will test whether the combination of a multivalent Th1 epitope anti-oncodriver DNA vaccine and HER2-pulsed IL-12 secreting dendritic cell (DC1) vaccine can improve complete pathologic response rates in HER2+ breast cancer (NCT03387553). A Phase II multi-site trial is ongoing to evaluate the safety of the DC1 vaccine compared to WOKVAC, with the purpose of preventing recurrence in patients with HER2 positive breast cancer (NCT03384914).

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#### Trastuzumab/Pertuzumab with HER2 HLA-DR Vaccine Therapy — Keith Knutson and Saranya Chumsri

Preclinical studies addressed the role of HER2 in the self-renewal capacity of tumor-initiating cells or cancer stem cells in breast cancer. A Phase I trial demonstrated that a multi-epitope HLA-DR vaccine, consisting of a pool of four HLA-DR-restricted epitopes combined with the immunoadjuvant GM-CSF, was well-tolerated and boosted T-cell immunity to HER2 in HER2+ breast cancer patients that were found to be disease free following completion of standard of care treatment. A BCRP-funded randomized Phase II clinical trial will evaluate whether boosting HER2-specific T cells during trastuzumab and pertuzumab maintenance therapy in patients with recurrent or metastatic HER2+ breast cancer (NCT03632941).

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### NOVEL TECHNIQUES IN TREATMENT

#### Targeted HER2 Radiotracer — Gary Ulaner

Growing evidence suggests that HER2 expression may change between primary HER2- lesions and HER2+ metastases, an example of tumor heterogeneity. A recently completed Phase I trial used a targeted HER2 radiotracer (89Zr-trastuzumab) to determine the proportion of patients with HER2-negative primary breast cancer who develop imagable HER2-positive metastases (NCT02065609).

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#### Polycationic Peptides for Fluorescence-Guided Surgery — Roger Tsien

AVB-620, a protease-activatable fluorescent 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 is ongoing (NCT03113825).

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**Fatty Acid Synthase Inhibitor — Ruth Lupu and Tufia Haddad**

A Phase II clinical trial is evaluating 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 (NCT03179904).

**Temozolomide Combined with T-DM1 — Patricia Steeg**

An FY05 BCRP Center of Excellence Award formed the first group to examine brain metastasis in a comprehensive multidisciplinary manner. A Phase III 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 whether the combination will prevent formation of new metastases in the brain.

**Pembrolizumab and Tremelimumab for Treatment of Oligometastasis — Andy Minn**

A Phase I clinical trial is underway to examine radiation to 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. A second Phase I trial has also started to test radiation in combination with dual immune checkpoint blockade, using tremelimumab (anti-CTLA-4) and MEDI14736 (anti-PDL1) for patients with metastatic breast cancer and other cancers (NCT02639026).

**Combining Aromatase and Src Inhibitors — Joyce Slingerland and Isabel Chu**

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. A Phase III trial has been completed that tested 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 (NCT01216176). The results are currently being analyzed.

**5-Fluoro-2’deoxyctydine (FdCyd) — Edward Newman**

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 (NCT01479348), and an NCI supported Phase II trial is ongoing (NCT00978250).

**Anti-Androgen Therapy (Enzalutamide) — Anthony Elias and Jennifer Richer**

Enzalutamide (Enza) is a potent inhibitor of androgen-induced proliferation of ER+ breast cancer cells, which express higher levels of androgen receptors and are commonly resistant to anti-estrogen therapy. Preclinical studies in ER+ breast cancer models demonstrated activity of Enza monotherapy and enhanced activity when combined with various endocrine therapies. A single-arm Phase II clinical trial is currently evaluating the tolerability and clinical activity of adding Enza to fulvestrant treatment in women with advanced ER and/or progesterone receptor positive breast cancers that are HER2 normal (NCT02953860). A second randomized and two-arm Phase II trial has been initiated to further evaluate the efficacy of fulvestrant plus Enza compared to single agent fulvestrant (NCT02955394).

**Meclofenamate for Brain Metastasis — Joan Massague**

This is 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, an FDA-approved non-aspirin, non-steroidal anti-inflammatory drug. As a result, a Phase I pilot clinical trial is underway to determine whether Meclofenamate can prevent new brain metastases in patients with recurrent or progressive brain metastasis from a solid primary tumor (NCT02429570).

**Aspirin as Adjuvant Therapy for Node-Positive Breast Cancer — Eric Winer and Michelle Holmes**

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 is underway (NCT02927249). Using invasive disease-free survival as the primary endpoint, the trial will assess adherence to and the 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**

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**

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 that is indicative of bone repair after treatment with the RON kinase inhibitor.

**Talazoparib — Dennis Slamon**

Preclinical studies supported the use of the novel PARP inhibitor, talazoparib, in non-BRCA mutant triple-negative disease and other luminal subtypes of breast cancer. A Phase Ib clinical trial evaluated the safety of talazoparib in combination with other breast cancer therapeutics, and has been expanded to a Phase II clinical trial in TNBC (NCT03499353).
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

Intraductal Techniques

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

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 enables an expanded...
Breast cancer cells enter the bloodstream. TMEM sites are correlated at sites called TMEM and spread elsewhere in the body. 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 publicly available.

**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 publicly 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.

**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 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.

**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 patient centric models before entering trials, work is 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 https://cdmrp.army.mil
or contact us at: usarmy.detrick.medcom-cdmrp.mbx.cdmrp-public-affairs@mail.mil
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