NOVEL INSIGHTS IN BREAST CANCER PROGRESSION REVEALED AT 2008 ERA OF HOPE MEETING

New Approaches Seek to Identify Therapeutic Targets and Novel Compounds to Prevent or Reduce Breast Cancer Metastasis

Baltimore, Md. – June 26, 2008 – The Department of Defense Breast Cancer Research Program (BCRP) will highlight the most recent research focusing on new approaches to combating breast cancer progression and metastasis this week at the 5th Era of Hope meeting. During the 4-day meeting being held June 25–28 at the Baltimore Convention Center, breast cancer survivors and researchers will assess and examine some of the new breakthroughs in cancer progression as well as reflect on the BCRP’s progress toward its vision of eradicating breast cancer, the most commonly diagnosed cancer among women in the United States (excluding skin cancer).

The majority of deaths due to breast cancer result from the formation of invasive tumors that infiltrate surrounding breast tissue and eventually move from the breast to distant organs such as lymph nodes, lung, liver, and bone. To date, there is no effective cure for metastatic breast cancer. Current treatments focus on controlling the growth of existing tumors and preventing the cancer from spreading further while at the same time minimizing side effects from the treatment. Often women with metastatic breast cancer will exhaust a treatment regimen that includes several different types of therapies over the course of their disease because the cancer cells become resistant to treatments. In promising research presented this week, scientists are exploring new ways to reduce the tumor cells’ resistance to antihormonal therapies, which may eventually suppress breast cancer metastases.

“The BCRP has supported translational research in an effort to accelerate the discovery of new therapies for breast cancer, such as the development of Herceptin, a revolutionary drug based upon an anti-HER2 antibody that kills breast cancer cells,” said Dr. Dennis Slamon of the UCLA’s Jonsson Comprehensive Cancer Center whose research led to the development of Herceptin. “As a result of that research, women with HER2-positive breast cancer are living longer. The encouraging research being presented this week will hopefully continue to further our understanding of breast cancer progression so that one day soon women will no longer suffer from this deadly disease.” The BCRP will demonstrate the progress made in research on breast cancer progression and metastasis in several symposia sessions in the meeting, including:

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• “Molecular Pathogenesis of Breast Cancer Progression,” Saturday, June 28 at 10:30 a.m.
• “Progress in Progression,” Thursday, June 26 at 10:30 a.m.
• “Threading the Needle: Targeting Breast Cancer Metastasis,” Thursday, June 26 at 2 p.m.
• “Center of Excellence Discussion: Spanning the Complexity of Brain Metastasis,” Friday, June 27 at 2:00 p.m.

Some of the latest research on breast cancer metastasis and progression at the meeting will be presented within the context of the following abstracts:

**Fly to Mouse: A New Approach to Cancer Metastasis – Ross Cagan, Mount Sinai School of Medicine**
Achieving long-term improvement in survival among cancer patients has proved to be difficult. Researchers have therefore taken a broader, combined whole-animal approach to examine the complexities inherent in cancer and associated metastasis. These researchers have undertaken a genetic and drug screening approach targeting cancer and metastasis using the fruit fly, *Drosophila*. They have modeled several cancers including breast, and have identified several pathways that mediate overgrowth and metastasis. Additionally, careful analysis of discrete tumors has suggested a novel model in which metastasis is the outcome of early, local interactions between normal and transformed epithelial cells specifically at tumor boundaries. Using robotics, the scientists have developed a method of high-throughput drug screening using *Drosophila* models of cancer and metastasis. This whole-animal approach helped identify several candidate compounds that suppress metastasis in the fly, at least one of which has also proven effective in reducing lung metastases in a mouse syngeneic model of breast cancer.

**Epigenetic Regulation of Breast Cancer Progression – Sam Thiagalingam, Boston University School of Medicine**
Transforming growth factor-beta (TGF-beta)–Smad signaling pathways play critical but opposing roles in both tumor suppression and metastatic cancer promotion – an early tumor suppressive and a late-stage pro-oncogenic role concomitant with a progressive increase in locally secreted TGF-beta levels. It has also been shown that high incidence of breast cancer metastasis is associated with an increase in phosphorylated Smad2 in the nucleus. These observations suggest that the TGF-beta–TGF-beta Receptor–Smad2 signaling axis is involved in breast cancer metastasis and is a legitimate target for therapeutic intervention. The results from these studies suggest that aberrant signaling events regulate epigenetic alterations to define altered gene function during breast cancer progression. Furthermore, by disrupting hyperactive TGF-beta signaling in breast cancer cells, the researcher have successfully reversed the metastatic properties of breast cancer cells suggesting that these approaches are amenable to therapeutic applications.

**The Suppression of Breast Cancer Metastasis by Bone Morphogenic Proteins – Robin Anderson, Peter MacCallum Cancer Centre**
To enhance the breast cancer community’s current understanding of the molecular events regulating metastasis, these researchers have used a mouse model of spontaneous breast cancer metastasis to reveal genetic determinants. They are currently investigating bone morphogenic protein-4 (BMP4), a cytokine involved in tissue patterning and morphogenesis, which had reduced expression in highly metastatic tumors and was further characterized for its role in metastasis. Preliminary results showed overall survival of mice bearing 4T1.2 primary tumors engineered to express exogenous BMP4 (4T1.2-BMP4) was significantly greater than those bearing the parental 4T1.2 tumors. This was attributed to decreased tumor cell escape from the primary site and a marked reduction in detectable secondary tumors in most mice. Similar results were obtained in mice bearing 4T1.2 tumors expressing BMP7 or both BMP4 and BMP7.

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The clinical efficacy of BMP4 as an antimetastatic therapy was also assessed by administration of recombinant BMP4 (rBMP4) to mice bearing 4T1.2 tumors. Mice receiving rBMP4 had a significant increase in overall survival compared with controls, suggesting that BMPs could be used as an adjuvant therapy for metastatic disease. Taken together, these results demonstrate a novel role for BMP4 and BMP7 as breast cancer metastasis suppressors.

The Evolution of Drug Resistance to Antihormonal Therapy Exposes a Vulnerability in Breast Cancer – V. Craig Jordan, Fox Chase Cancer Center

The ubiquitous application of selective estrogen receptor modulators (SERMs) and aromatase inhibitors for the treatment and prevention of breast cancer has created a significant advance in patient care. However, one of the consequences of prolonged treatment with antihormonal therapy is the development of drug resistance. Nevertheless, the systematic description model of drug resistance to SERMs and aromatase inhibitors has resulted in the discovery of a vulnerability in tumor homeostasis that can be exploited to improve patient care. Laboratory studies of exhaustive antihormonal therapy demonstrate that there are at least two phases of resistance to SERMs (tamoxifen and raloxifene) and to estrogen withdrawal (aromatase inhibitors). In Phase 1 drug resistance, estrogen or a SERM promote tumor growth, but in Phase 2 drug resistance, estrogen induces apoptosis. Understanding of the new biology of estrogen action has clinical relevance. It is clear that drug resistance to antihormones evolves so that eventually the cells change to create novel signal transduction pathways for enhanced estrogen (GPR30 plus ER) sensitivity, a reduction in progesterone receptor production, and an increased metastatic potential. These researchers have initiated a major collaborative program of genomics and proteomics using laboratory models to map the mechanisms of subcellular survival and apoptosis in breast cancer. The laboratory program is integrated with a clinical program that seeks to determine a minimum dose of estrogen necessary to create objective responses in patients who have succeeded and failed two consecutive antihormonal therapies. When the program is complete, new knowledge will be available to improve clinical care for the long-term maintenance of patients on antihormonal therapy.

About the BCRP and Era of Hope

The Department of Defense BCRP is a congressionally mandated program managed by the U.S. Army Medical Research and Materiel Command’s Congressionally Directed Medical Research Programs (CDMRP). The BCRP seeks to eradicate breast cancer by funding innovative, high-impact research and has integrated the ideas and perspectives of breast cancer survivors into all aspects of the program. As the second largest source of breast cancer research in the United States, the BCRP has received over $2 billion in congressional appropriations since its inception in 1992, granting over 5,000 unique awards that fulfill unmet needs in breast cancer research. The success of these grants is illustrated in part by the fact that over 10,000 publications have resulted from BCRP-funded research, more than 11,000 abstracts have been published; and over 400 patents and licensures have been issued. In 2008, the program received $138 million in congressional appropriations to be invested in breast cancer research. For more information about the BCRP, please visit http://cdmrp.army.mil/bcrp/.

The BCRP is hosting its fifth international Era of Hope meeting, a unique forum for scientists, clinicians, breast cancer survivors and advocates, policy makers, and the public to come together and discuss the latest findings in breast cancer research and future directions to eradicate this disease. More than 1,600 awardees, researchers, breast cancer survivors and health advocates will attend this year’s Era of Hope, which will feature more than 1,200 abstracts focusing on the program’s breakthroughs in the prevention, detection, diagnosis, and treatment of breast cancer as well as quality of life issues. For more information about the Era of Hope meeting, please visit: https://cdmrpcures.org/.

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