LATEST FINDINGS ON BREAST CANCER STEM CELLS
FEATURED AT 2008 ERA OF HOPE MEETING

Research Shows Breast Cancer Stem Cells Can Originate in Other Locations in the Body

Baltimore, Md. – June 26 2008 – At the 5th Era of Hope meeting, sponsored by the Department of Defense Breast Cancer Research Program (BCRP), new data are being presented this week on the role of stem cells in breast cancer. During the 4-day meeting being held June 25–28 at the Baltimore Convention Center, breast cancer survivors and researchers will review the new theories on breast cancer stem cells while reflecting 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).

In new studies being highlighted at the meeting, researchers are presenting data that demonstrates how cancer-promoting and cancer-initiating stem cells, while mainly residing in the organ of cancer origin, can also be derived from ectopic locations. In another study, the double-hit molecular therapy by the self-assembled Herceptin-nanovector-miRNA shows promise as a novel treatment for erbB2(+) breast cancer through inhibiting breast cancer stem cells.

“The BCRP has developed a multidisciplinary portfolio that encompasses a wide variety of research, including research that examines the potential benefits and implications of breast cancer stem cells,” said CAPT Melissa Kaimé, Deputy Director of the Congressionally Directed Medical Research Programs (CDMRP) which manages the BCRP. “Through BCRP-supported stem cell research, we hope to attain a greater understanding of stems cells and their role in breast cancer and now as new, promising research is released, we move closer and closer to that goal.”

The BCRP will showcase its progress in breast cancer stem cell research in a symposia session entitled “Exploring the Origins of Breast Cancer Stem Cells” scheduled to be held on Thursday, June 26 at 10:30 a.m. Some of the latest data on stem cell research at the meeting will be presented within the context of the following abstracts:

Cancer-promoting and Initiating Stem Cells Can be Derived from Ectopic Locations in Inflammatory and Other Breast Cancers - Sanford H. Barsky, Ohio State University

Although human breast cancer is all too common, circumstantial evidence exists on a cellular level to suggest that cancer transformation is a rare event.

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Even in the setting of inherited breast cancer (e.g. BRCA1 when all the cells of the breast contain the inherited BRCA1 mutations), transformation on a cellular level is still rare. This suggests that only certain cells are capable of cancer initiation and promotion. Cancer-promoting and cancer-initiating stem cells, while mainly residing in the organ of cancer origin, can also be derived from ectopic locations. In a study of a registry of transplant recipients who had received sex-mismatched bone marrow and other organ transplants for various diseases and later developed secondary solid cancers including breast cancer, cancer-promoting stem cells giving rise to lymphocytes, fibroblasts, myofibroblasts, tissue macrophages and endothelial cells and rarely, cancer-initiating stem cells were observed within the secondary solid cancer that were of donor origin. Carrying forward these observational studies made in humans to testing these hypotheses experimentally in mouse models, we conducted bone marrow transplantations in transgenic mice genetically engineered to develop breast cancer. Being able to mark the donor bone marrow enzymatically, we were able to study the breast cancers that developed in the mammary gland for the presence of stem cells derived from the bone marrow. Using either the bitransgenic MMTV-pymT/ROSA26 or the MMTV-erbb2/neu/ROSA26 models as donors and either lethally irradiated wild type or single unmarked transgenics as recipients, we were able to demonstrate that the breast cancers that emerged contained significant percentages of tissue macrophages, lymphocytes, fibroblasts, myofibroblasts and endothelial cells, which presumably represented the progeny of cancer-promoting stem cells of donor origin. Rare cancer-initiating stem cells of donor origin were also observed. These ectopically-derived cells may affect breast cancer progression differently than those of endogenous breast origin. In another experimental model system, we used a human xenograft of inflammatory breast cancer (MARY-X) which demonstrated, as in patients, florid lymphovascular tumor emboli within lymphovascular channels. These emboli which were resistant to chemotherapy, exhibited a prominent stem cell-like phenotype with high expression of CD133, CD44, ALDH1, oct-4, nanog, sox-2, stellar, rex-1, H19 and nestin, suggesting that the lymphovascular tumor emboli, like the human embryonal blastocyst, are derived from stem cells locked in self-renewal. In parallel bone marrow transplant experiments, some of the endothelial cells which lined the channels containing the tumor emboli exhibited evidence of bone marrow origin. Inflammatory breast cancer in humans oftentimes consists of only florid lymphovascular tumor emboli without the presence of a pre-cancerous or invasive cancerous mass in the breast and therefore may reflect the presence of both cancer-promoting as well as cancer-initiating stem cells derived from ectopic locations.

**DCIS Stem Cells: Investigating the Origin of the Invasive Phenotype – Lance Allen Liotta, George Mason University**

Scientists are testing the hypothesis that ductal carcinoma in situ (DCIS) neoplastic cells already possess the full capability to invade and perhaps metastasize, but that this malignant potential is delayed or held in check because the DCIS cells are confined in the unique niche microenviroment of the duct. The specific aims of this study include: (1) to microdissect in vitro living human DCIS structures consisting of a duct wall segment and its contained DCIS cells; (2) to test the malignant phenotype of the harvested DCIS within immunodeficient SCID mice; (3) to map the proteomic signal pathway profile of the microdissected human DCIS compared with matched invasive, normal, hyperplastic, and benign-appearing breast tissue; and (4) to derive continuous lines of DCIS stem cells. Although it is too early in the project time line to report the success rate for generating invasive tumors from putative DCIS stem cells derived from DCIS organoids, the preliminary data to date support the conclusion that the differentiated and metastatic potential of an individual patient's breast cancer is predetermined at the level of DCIS. The demonstration that DCIS cells already possess the capacity to invade, and perhaps metastasize, can profoundly alter future strategies for cancer screening and treatment.
It will be important to identify the molecular and tissue structural factors that keep the DCIS cancer stem cells in check. The availability of continuous lines of human DCIS stem cells can become the foundation for a whole field of mechanistic and therapeutic studies.

**Mammary Stem Cells and Residual Neoplastic Disease – Lewis A. Chodosh, University of Pennsylvania School of Medicine**

A cardinal feature of human breast cancers is the survival and persistence of residual neoplastic cells in a presumed quiescent state following the apparently successful treatment of the initial tumor. Ultimately, these residual cells re-emerge from their dormant state and resume growth, leading to cancer recurrence. The ability of residual neoplastic cells to survive for many years has raised the possibility that these cells may share important properties with mammary stem cells. Since the ability to self-renew is common to both normal stem cells and cancer cells, and since several signaling pathways implicated in cancer have also been implicated in stem cell self-renewal, it has further been proposed that normal stem cells may represent a preferred target for transformation. To better define the molecular and cellular events that contribute to breast cancer recurrence, researchers have developed a series of doxycycline-inducible transgenic mouse models that display many features of human breast cancer progression, including metastasis, residual neoplastic disease, and recurrence. Following induction with doxycycline, bitransgenic animals develop invasive mammary adenocarcinomas. Subsequently, the majority of these tumors regress to a clinically undetectable state following doxycycline withdrawal and oncogene downregulation. However, many fully regressed tumors spontaneously recur in the absence of oncogene expression over periods of up to a year, ultimately resulting in the death of the animal. The researchers hypothesize that the population of residual neoplastic cells that survive oncogene downregulation and persist in the mammary gland following tumor regression are enriched for cells that share critical features with mammary stem cells and/or cancer stem cells. The experiments supported by this proposal attempt to determine the relationship between residual neoplastic cells, stem cells, and cancer stem cells using functional tests and to thereby analyze properties of residual neoplastic cells that are relevant to tumor recurrence. Studying residual neoplastic cells to determine their potential relationship to mammary stem cells or cancer stem cells may shed light on the role of these cells in breast cancer progression and may provide new ways to prospectively identify tumors posing greater risk for recurrence while also facilitating the development of more appropriate therapies targeted against this critical subpopulation of tumor cells.

**Double-Hit Molecular Therapy for erbB2(+) Breast Cancer by the Self-Assembled Herceptin-Nanovector-miRNA Inhibits Breast Cancer Stem Cells – Liang Xu / Min Zhang, University of Michigan**

MicroRNAs (miRNAs) are a conserved class of noncoding RNAs that regulate gene expression post-transcriptionally. miRNAs regulate a variety of biological processes, including developmental timing, signal transduction, tissue differentiation and maintenance, disease, and carcinogenesis. Emerging evidence demonstrates that miRNAs also play an essential role in stem cell self-renewal and differentiation by negatively regulating the expression of certain key genes in stem cells. This study shows that miR-34 potently suppresses genes involved in cancer stem cell self-renewal and survival and inhibits breast cancer mammosphere growth and tumor formation, indicating that tumor suppressor miRNAs such as miR-34 may hold significant potential as novel molecular therapies for cancer. However, delivering the miRNA-based therapeutics efficiently and specifically to tumor and its metastases remains a great challenge. To overcome this challenge, these researchers have developed a self-assembled nanoparticle system. This system shows promising efficiency in targeted delivery of p53 gene and Ras/HER2-antisense oligonucleotides to breast tumors and is now in Phase I clinical trial.
These self-assembled nanovectors have novel nanostructure that resembles a virus particle with a dense core enveloped by a membrane coated with targeting molecules spiking on the surface. In the current study funded by a Concept Award, researchers established and optimized the nanovector system targeted by anti-erbB2 antibody, Herceptin, for tumor-targeted delivery of miRNAs to erbB2(+) human breast cancer. Preliminary results suggest that the double-hit molecular therapy by the self-assembled Herceptin-nanovector-miRNA shows promise as a novel treatment for erbB2(+) breast cancer via inhibiting breast cancer stem cells.

**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/](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/](https://cdmrpcures.org/).

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