



NEW THERAPEUTIC ADVANCEMENTS SHOWCASED AT 2008 ERA OF HOPE MEETING

Synergies of New Combination Therapies Hold Promise of Suppressing Advanced Breast Cancers

Baltimore, Md. – June 26, 2008 – At the 5th Era of Hope meeting, sponsored by the Department of Defense Breast Cancer Research Program (BCRP), new research is being presented this week on novel approaches to treating 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 latest data on new therapeutic agents 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).

Some of the new approaches to treating breast cancer that hold promise include a PRIMA-1 plus 2aG4 combination therapy, WX-671 in combination with capecitabine, nanoparticles carrying LHRH analog and doxorubicin, and a combination treatment of selective tumor vascular thrombosis and protease-activated prodrug.

“Since its inception, the BCRP has devoted itself to discovering potential treatment options by identifying and fulfilling unmet needs in breast cancer research,” said Dr. Dennis Slamon, Director of Clinical/Translational Research at UCLA's Jonsson Comprehensive Cancer Center. “The novel therapeutic combinations being showcased at the Era of Hope have the ability to define new treatment strategies for the inhibition of advanced breast cancers, one of the main areas of focus in breast cancer research today.”

The BCRP will showcase its progress in identifying new breast cancer treatment options in a symposium session entitled “Targeted Therapeutics: Are We Hitting the Mark?” scheduled to be held on Thursday, June 26 at 2 p.m. and a controversy session entitled “Controversial Issues in Breast Cancer Treatment” scheduled for Thursday, June 26 at 4:15 p.m. Some of the latest research on new therapies under investigation at the meeting will be presented within the context of the following abstracts:

Antimetastatic Therapy with WX-UK1 and WX-671 for the Treatment of Breast Cancer: Phase 1 Results and Phase 2 Design – Bernd Muehlenweg, Willex AG

The primary cause of death in patients with malignant solid tumors is not the primary tumor but rather distant metastases. Urokinase-type plasminogen activator (uPA) and its inhibitor PAI-1 (plasminogen activator inhibitor 1) play a key role in tumor invasion and metastasis.

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Currently, uPA and PAI-1 are the only biomarkers that have been validated by the European Organization for the Treatment and Research of Cancer at the highest level of evidence (LOE I) with regard to their clinical utility in breast cancer prognosis. WX-UK1 is an active site competitive inhibitor of serine proteases with an inhibition constant (Ki) for human uPA in the submicromolar range. In preclinical animal tumor models, parenterally administered WX-UK1 and its orally administered prodrug WX-671 reduce the growth rate of implanted tumors, inhibit their invasion into nearby lymph nodes and metastasis. WX-UK1 in combination with capecitabine (a chemotherapy drug) was investigated in a Phase 1 study to determine the safety, tolerance, maximum tolerable dose (MTD), and pharmacokinetics in patients with advanced malignancies. No dose-limiting toxicities were observed during the entire treatment period, and no MTD could be identified in this study. This demonstrates that the combination was well tolerated by all patients for the duration of the study. Some patients showed a partial response during the study, which is encouraging as all these patients had advanced, metastatic tumors for which no standard treatment is efficacious. In a Phase 2 trial (two-arm, double-blind, multicenter, randomized trial), the efficacy of the oral prodrug of WX-UK1, called WX-671, will be tested in combination with capecitabine vs. capecitabine monotherapy in first-line HER2-negative metastatic breast cancer patients. Each arm will enroll 50 patients.

A Novel and Effective Combination Targeting Therapy for Advanced Human Breast Tumors – Yayun Liang, University of Missouri

Mutations in the tumor suppressor p53 facilitate tumor cell survival and resistance to chemotherapeutic drugs. Consequently, restoring p53 function within tumors is a promising strategy for targeted cancer therapy. Furthermore, vascular targeting agents for treatment of cancer are designed to cause selective shutdown of tumor blood vessels and offer yet another opportunity to reduce tumor load. Anionic phospholipids (AP), exposed on the surface of tumor endothelial cells, serve as a marker for vascular disruption. Thus, treatment strategies that incorporate both of these pathways may result in improved and more potent responses. The aim of this study was to determine whether combination therapy targeting mtp53 and tumor blood vessels could be an effective therapeutic strategy for suppression of advanced breast cancer. Researchers tested whether the therapeutic effects of PRIMA-1, which reactivates mtp53 and induces tumor cell apoptosis, and 2aG4, a monoclonal antibody that disrupts tumor vasculature by binding to AP on tumor endothelial cells, causes selective shutdown of tumor blood vessels. Two advanced breast tumor models that express mtp53, and are either Her2/neu positive (BT-474) or negative (HCC-1428), were used to evaluate this novel combination therapy. The researchers' results indicate that PRIMA-1 plus 2aG4 combination therapy has a complementary and potent antitumor activity and could define a new strategy for suppression of advanced breast cancers.

LHRH and Doxorubicin Conjugated Gold Nanoparticles for Breast Cancer Treatment – Sham S. Kakar, University of Louisville

While the primary treatment for cancer (cytoreductive surgery followed by adjuvant chemotherapy, radiotherapy, or both) is successful in the majority of cases, it is cytotoxic to normal cells and organs. The purpose of this study was to develop a method to treat breast cancer more specifically and to minimize the systemic toxicity. Direct targeting of cancer cells can be achieved by using agents specifically directed to binding sites on cancer cells, such as carbohydrates, lectins, surface proteins, and receptors. LHRH receptors are present in hormone-related tumors, including breast cancer. In normal tissues, LHRH receptors are not expressed or are expressed at an undetectable level. By coupling these receptors to nanoparticles, breast cancer and their metastases can be targeted directly. The researchers hypothesized that targeting the LHRH receptor using nanoparticles carrying the LHRH analog and a cytotoxic agent (doxorubicin) would enhance drug uptake by cancer cells with reduced toxicity to normal cells.

Studies were performed in vitro and in vivo and results suggest that the LHRH analog “[D-Trp6]LHRH” can be specifically used to target breast cancer cells, delivering anticancer agents to induce cell death.

Precision Guided Cancer Therapy: Synergism of Selective Tumor Vascular Thrombosis and Tumor Microenvironment Activated Prodrug – Cheng Liu, Scripps Research Institute

Targeted drug activation at selected sites promises reduced toxicity and enhanced efficacy. In this study, researchers tested a bipartite drug delivery-activation system that employs selective tumor vascular targeted induction of an endogenous coagulation protease cascade followed by administration of a protease-activated prodrug. The efficacy of this strategy has been demonstrated by a fibronectin motif and tissue factor extracellular domain fusion protein that specifically activates coagulation on the tumor vascular endothelial surface when certain integrins, such as $\alpha\beta3$ and $\alpha5\beta1$, are expressed and exposed. The activation of the coagulation cascade and tumor vascular thrombosis as well as subsequent activation of thrombolytic pathways leads to the explosive amplification of serine protease cascades and local proteolytic activity within the tumor vasculature. This tumor-specific proteolytic activity has also been exploited for targeted local prodrug activation. In rodent and human tumor models, the combination treatment of selective tumor vascular thrombosis and protease-activated prodrug demonstrated a profound synergism. An even more robust and sustained tumor vascular thrombosis was observed compared to selective tumor vascular thrombosis alone. The activation of local tumor vascular thrombosis substantially increased prodrug activation and retention in tumors. Importantly, the activated prodrug eliminated the remaining tumor cells at the rim of tumors that do not depend on neo-angiogenesis for survival. This coordinated attack on tumors resulted in complete tumor eradication with no apparent toxicity. The synergistic targeted activation of coagulation and prodrug possesses interchangeable targeting potentials with different tumor vascular specific molecules and thus may represent a general therapeutic strategy for breast cancer 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/>.