"An international scientific symposium for interaction and exchange among basic scientists and clinicians in breast cancer."

SAN ANTONIO BREAST CANCER SYMPOSIUM®

UT Medicine CTRC Health Science Center San Antonio | AACR American Association for Cancer Research | Baylor College of Medicine

Newsletter 2014

ISSUE 2

Plenary Lecture #2: Patient-Derived Xenografts: Models for Prevention and Treatment of Metastasis

Alana L. Welm, PhD

Since earlier studies looking at grafts of human breast cancer (BC) tumors under the skin of mice did not systematically investigate the problem of metastasis, Dr. Alana Welm and her colleagues wondered what would happen if tumors were implanted in the mammary fat pads of the animals, without culturing them in the laboratory first.

"They did metastasize, so that was probably the most exciting part," Dr. Welm said. This sparked her work with patient-derived xenograft (PDX) models, and in the determination of just how closely related the tumors in mouse models are to those in human patients.

On Thursday, Dr. Welm will discuss some important similarities between the mouse models and the humans from which the tumors originated. For one, metastasis to the organs in the mice was found to be similar to the affected organs in the human patients. Also, while the percentage of tumors that actually grew in the animal after implantation was low (≈30%), the ability of the tumor to grow correlated to the aggressiveness of the tumor in the human. Only the more aggressive tumors grew and metastasized in the mouse after transplantation. So, can these types of discoveries be used in the clinical setting to assess the likelihood of a tumor to metastasize? "Of course it's not practical to implant everyone's tumor in a mouse to see how aggressive it is, but it gives us a way to assess prognosis and to see if we can figure out which drugs might be the most effective for that particular type of tumor," Dr. Welm said.

But after implantation into the mouse, some tumors stop growing and regress. Does a microenvironment populated with human cells better support tumor growth than one with mouse cells? The answer is yes, and Dr. Welm's laboratory found that when the human tumor was implanted in the mouse along with human mesenchymal stem cells, the human cells did a better job of recruiting mouse-derived blood vessels to provide nutrients and oxygen to the tumor.

Another advantage of PDX models is that tumors grow at a rate more similar to the rate of growth in the human body, compared to cell line xenografts. Therefore, adding preclinical drug testing in PDX models to preexisting cell culture screening and cell line xenograft testing is just one other way PDX models can improve the ongoing development of new and effective BC therapies.

Thursday, December 11th - 9:00am - Hall D

Issue at a GLANCE

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Scan the QR code to hear brief interviews and commentaries from faculty who presented this year's hot topics and plenary lectures as they become available during the Symposium.

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Symposium UPDATES

POSTER SESSION 3
THURSDAY, DEC 11TH

POSTERS WITHDRAWN

- P3-04-08
- P3-04-13
- P3-05-05
- P3-06-18
- P3-07-12
- P3-07-33
- P3-09-03
- P3-13-03
- OT2-2-04

PRESENTING AUTHOR CHANGE

- OT2-4-02 – will be presented by Dr. Kim
- P3-05-21 – will be presented by Professor Leonie Young
- P3-05-22 – will be presented by Professor Leonie Young

POSTER SESSION 4
FRIDAY, DEC 12TH

POSTERS WITHDRAWN

- P4-01-05
- P4-04-22
- P4-11-34

PRESENTING AUTHOR CHANGE

- P4-05-02 – will be presented by Dr. Benford Mafuvadze
- P4-15-06 – will be presented by Dr. Tiziana Triulzi
- P4-11-34 – will be presented by Dr. Nur Ais

** At Press Time*

Scholarship Recipient

Demetrios Simos, MD is a recipient of the SABCS Clinical Scholar Award who was inadvertently left out of Issue 1 of the Newsletter.

AACR Outstanding Investigator Award for Breast Cancer Research

Origin of Metastatic Traits in Breast Cancer

Dr. Yibin Kang
Thursday, December 11, 2:15 pm, Hall D

The AACR Outstanding Investigator Award for Breast Cancer Research, funded by Susan G. Komen®, recognizes an investigator of no more than 50 years of age whose novel and significant work has had or may have a far-reaching impact on the etiology, detection, diagnosis, treatment, or prevention of breast cancer. Such work may involve any discipline across the continuum of biomedical research, including basic, translational, clinical and epidemiological studies.

Dr. Yibin Kang is honored for his seminal work in breast cancer metastasis, which has had substantial far-reaching impacts on developing new ways to prevent or treat breast cancer metastasis.

Highly notable contributions of Dr. Kang's research focus on the topic of tumor-stromal interaction in organotropic metastasis of breast cancer, particularly bone metastasis. He established a series of elegant mouse models to dissect the molecular dynamics and signaling activities of tumor cells as they disseminate to bone, break out of dormancy, and establish overt lesions. In conjunction with these mouse models, he used advanced imaging methods to show for the first time in vivo that osteolysis of bone by osteoclasts stimulated by metastatic tumor cells releases TGFβ to promote bone metastasis. He has made several other important contributions to the elucidation of bone metastasis, which occurs in greater than 70% of breast cancer patients, and has also established new targets for therapeutic intervention.

Dr. Kang received his bachelor's degree from Fudan University in Shanghai in 1995. After completing his graduate study at Duke University in 2000, Dr. Kang became an Irvington Institute postdoctoral fellow, under the mentorship of Dr. Joan Massagué, at the Memorial Sloan-Kettering Cancer Center where he pioneered a functional genomic approach to elucidate mechanism of breast cancer metastasis. Dr. Kang joined the faculty of Princeton University as an Assistant Professor of Molecular Biology in 2004 and is currently the Warner-Lambert Parke-Davis Professor of Molecular Biology.

Predicting Response to Hormonal Therapies

Focus on a number of molecular profiles, multigene assays, and genetic mutations in estrogen receptor-positive (ER+) breast cancer (BC) has led to deeper associations with prognosis and response to hormonal treatments.

On Wednesday morning, Dr. Rinath Jeselsohn presented findings from the TransCONFIRM study. Her group wanted to identify a molecular profile that could predict response of metastatic disease to fulvestrant in patients who developed recurrent BC. They identified a potential signature of 37 genes that clustered patients into two groups in response to fulvestrant. One gene associated with decreased progression-free survival was found to be TFAP2C, which encodes for the transcription factor AP-2 γ. High mRNA and protein levels of AP-2 γ correlated with decreased response to fulvestrant. "A follow-up study on a second independent data set is required to validate the correlation," Dr. Jeselsohn stated.

Next, Dr. Obi Griffith presented information about a gene study using targeted massively parallel sequencing on DNA samples from patients treated with 5 years of tamoxifen and followed for over 10 years. "We identified some novel hotspots, such as the CBFB splice site mutation," he said. They also found that mutations in DDR1 and NF1 were predictive of worse outcomes, while some genes such as ARID1B were associated with better relapse-free survival and BC-specific survival.

Dr. Michael Dixon presented data about genomic characterization in 17 postmenopausal women with ER+ BC treated with neoadjuvant letrozole. In addition to baseline analysis, "you need to analyze the cancer during therapy because it changes," he said. Dr. Dixon described a 4-gene model using 2 genes at diagnosis (IL6ST and NGFRAP) and 2 genes at 14 days (MCM4 and ASPM) that could potentially predict response to letrozole with a high degree of accuracy. His group found that in the training set, accuracy for predicting response was as high as 96%, and 93% in the validation set.

Emerging Immunotherapeutic Strategies: HER2-TDB and Pembrolizumab

A tremendous amount of work in breast cancer (BC) immunology has led to a better understanding of immunogenic tumors, and the development of T cell-targeted therapies. Taking note of similarities between triple-negative BC and other forms of cancer has also moved immune therapies forward, raising the question of potential rational combination therapies.

Dr. Teemu Junttila presented data about the development of HER2-TDB, a potent T cell-dependent bispecific antibody targeting HER2+ BC. "The in vivo activity of HER2-TDB is pretty striking," he said. In MMTV-huHER2 genetically engineered mouse models, tumor regression of >1000 mm^3 was seen, followed by significant increases in CD45+, CD8+, and IFNg+CD8+ cells in the tumors.

Combination studies using HER2-TDB and anti-PD-L1 saw enhanced inhibition of tumor growth and increased response rates. The next step would be to evaluate safety using appropriate preclinical models, he concluded.

Pembrolizumab, a drug currently approved for treatment of melanoma, was discussed by Dr. Rita Nanda. Her study of 32 heavily pretreated women with PD-L1-positive triple-negative BC saw an overall response rate of 18.5%. The drug appeared relatively safe and tolerable, with the most commonly reported adverse events being arthralgia, fatigue, myalgia, and nausea. Potentially immune-mediated events included pruritus and hypothyroidism. Five women developed an adverse event that was grade 3 or higher. Dr. Nanda said that a phase II study is planned for the first half of 2015.

Discussant Dr. Nora Disis heralded combination therapy. She mentioned that in some diseases, like melanoma, patients are already receiving combination therapy, and responding at rates of 50% to 60%. "Onward with the rational combinations so we can drive that response rate up," she said after pointing out that the biology, response rates, and toxicities seen in BC appear similar to those of other diseases.

Distinctions Between Invasive Lobular Cancer and Infiltrating Ductal Cancer

Should infiltrating ductal cancer (IDC) and invasive lobular cancer (ILC) be treated differently? Since lobular breast cancers (BC) make up only 5% to 10% of all BC cases, there hasn't been much effort to treat them with a different strategy. But now, an increasing number of molecular and treatment-response studies are finding characteristics that set ILC apart from IDC.

"Lobular breast cancer is a molecularly distinct disease," Dr. Giovanni Ciriello said. He and his group wanted to see what drives tumorigenesis in ILC, and what features differentiate it from invasive ductal carcinomas. According to Dr. Ciriello, 83% percent are luminal type A BC. He discussed a number of specific molecular characterizations in ILC that his group identified, such as CDH1 loss-of-function mutations, FOXA1 mutations, lack of GATA3 mutations, and PTEN loss-of-function mutations. Further, he showed that luminal type A ILC shows increased RTK/AKT activation compared to luminal type A IDC, which opens the door to a therapeutic opportunity for AKT inhibitors in ILC.

Later, Dr. Michael Knauer presented data from the Austrian Breast and Colorectal Cancer Study Group (ABCSG). ABCSG-8 was a study that randomized patients to either 5 years of tamoxifen or 2 years of tamoxifen followed by 3 years of anastrazole. They found that disease-free survival (DFS) and overall survival was significantly improved in patients on anastrazole who had ductal cancer, but not lobular cancer. Even after 11 years of follow-up, they did not see a difference between the treatments in patients with ductal cancer. However, the hazard ratio of 0.56 in lobular cancer was significant. Using PAM50-based intrinsic subtyping, Dr. Knauer reported the interesting finding that the benefit of anastrazole (compared to tamoxifen) was confined to only luminal type B lobular cancer, where the hazard ratio for DFS was 0.35 and 0.32 for overall survival.

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