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MEETING REPORT

HIGHLIGHTS FROM THE AACR SPECIAL CONFERENCE ON "ADVANCES IN BREAST CANCER RESEARCH: GENETICS, BIOLOGY AND CLINICAL APPLICATIONS"

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SUMMARY

The American Association for Cancer Research (AACR) organized a Special Conference on "Advances in Breast Cancer Research: Genetics, Biology and Clinical Applications" on October 13-16, 2009, held in the Hyatt Regency Mission Bay Spa and Marina, San Diego, California, USA. The conference was organized under the category of special conferences. The objective of the conference was to discuss recent advances, including discoveries in genetics, cell and molecular biology, that are relevant to mammary development, transformation and breast cancer progression. This report provides a comprehensive outlook of the proceedings conducted during the conference, which addressed several aspects of breast cancer research under distinct theme sessions. These included seven sessions, namely, stem cell biology, genetics and breast cancer risk, phosphatidylinositol 3-kinase signaling, translational research, determinants of breast cancer risk, tumor microenvironment, tumor dormancy and metastasis, and basal-like breast cancer, mouse models for breast cancer, genomic and proteomic approaches to tumor profiling, metastasis and breast cancer progression, oncogene signaling and the influence of tumor microenvironment on breast carcinogenesis. All these topics were correlated with other areas of science, including state-of-the-art imaging methods and the latest in molecular therapeutics for breast cancer. The conference included as many as 28 invited talks of eminent scientists who shared their experiences. In addition to a keynote address, the deliberations of the conference included a special theme on the Army of Women from the Susan Love Foundation. Over 400 researchers, including a large number of clinicians, biologists and chemists, attended the conference as delegates, many of whom presented their work as posters (about 200) in 2 sessions. As the participants represented about 40 nations, the conference truly wore an international perspective.

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INTRODUCTION

The American Association for Cancer Research (AACR) Special Conference on "Advances in Breast Cancer Research: Genetics, Biology and Clinical Applications", was held on October 13-16, 2009, at the Hyatt Regency Mission Bay Spa and Marina in San Diego, California, USA. The conference was chaired jointly by Dr. Carlos Arteaga of the Vanderbilt-Ingram Cancer Center, Nashville, TN, Dr. Lewis Chodosh of the University of Pennsylvania, Philadelphia, PA, and Dr. Kornelia Polyak of the Dana-Farber Cancer Institute, Boston, MA. The objectives of the conference were clearly drawn to discuss the latest discoveries in genetics, cell biology and molecular biology that are relevant to mammary development, transformation and breast cancer progression. The report provides a comprehensive outlook of the conference proceedings.

OPENING REMARKS AND KEYNOTE ADDRESS

The conference opened on the everning of the first day (10/13/09) with the welcome note from the chairpersons, who explained the

themes and gave a brief overview of the scientific program. The speaker of the keynote address, Prof. Michael Stratton of Wellcome Trust Institute, Cambridge, U.K., was introduced. Dr. Stratton delivered his talk on patterns of somatic mutations in human cancer genomes. He explained the mutations in a subset of genes that confer a growth advantage and stated that systematic resequencing of cancer genomes for mutations would lead to the discovery of many additional cancer genes (more than 1,000 somatic mutations found in 274 megabases [Mb] of DNA corresponding to the coding exons of 518 protein kinase genes in 210 diverse human cancers). He suggested that most somatic mutations are likely to be "passengers" that do not contribute to oncogenesis. However, there was evidence for "driver" mutations contributing to the development of the cancers studied in approximately 120 genes (1, 2). He also proposed that systematic sequencing of cancer genomes therefore reveals the evolutionary diversity of cancers and implicates a larger repertoire of cancer genes than previously anticipated. The lecture received spontaneous applause from the audience, who later participated in a lively discussion. The discussions continued in the opening reception that followed the keynote address.

SESSION 1: STEM CELLS (DAY 2)

Dr. Jeffrey Rosen, the C.C. Bell Professor of Molecular and Cellular Biology at Baylor College of Medicine, Houston, TX, chaired this session on stem cells, which included three invited talks including his own. The first speaker, Dr. Max Wicha, Director, the University of Michigan Comprehensive Cancer Center at Ann Arbor, MI, delivered his presentation on targeting the breast cancer stem cell niche. The self-renewal and differentiation of normal stem cells is partly regulated by extrinsic signals originating in their environment, which has been termed the "stem cell niche". Dr. Wicha explained that they have developed in vitro systems and mouse xenograft models to examine the interaction between breast cancer stem cells (CSCs) and bone marrow-derived mesenchymal stem cells (MSCs). He also demonstrated that both of these cell populations are organized in the cellular hierarchy in which primitive aldehyde dehydrogenase-expressing MSCs regulate CSCs through cytokine loops involving IL-6 and CXCL7. The MSC/CSC niches were identified in tumor xenografts, as well as in primary human breast cancers. He stated that other cytokine loops that regulate CSC self-renewal were detected. Expression profiling identified CXCR1, a cellular receptor for the inflammatory cytokine IL-8 as being overexpressed in the CSC population. He concluded his talk by saying that the CSC niche contains cellular elements including bone marrow-derived MSCs, as well as cytokine loops. Strategies, such as CXCR1 blockade, which interfere with these loops may provide a novel means of targeting and eliminating CSCs.

Dr. Rosen, who gave the next lecture of the session, spoke on the intrinsic therapeutic resistance of breast cancer tumor-initiating cells (TICs). He stated that many patients relapse after an initially favorable response to chemotherapy and radiation therapy (3, 4). The relapses may be due to acquired resistance, resulting in decreased overall sensitivity to therapy over the passage of time and a subpopulation of cells with tumorigenic potential that are intrinsically resistant to therapy. He also confirmed that they have developed a unique p53-null murine breast cancer model to distinguish the tumor-initiating subpopulation of cells from others. The TICs expressed higher levels of DNA damage response genes and DNA repair genes. Post-treatment residual tumors contained a higher fraction of claudin-low cells, consistent with therapy-mediated enrichment of resistant cells. These cells expressed higher levels of markers characteristic of epithelial-to-mesenchymal transition (EMT). In claudin-low tumors developed in the p53-null murine breast cancer model, there was a concomitant loss of specific microRNAs (miRNAs) known to regulate EMT. A small subset of cells expressing mesenchymal markers appear to be responsible in part for the intrinsic resistance to therapy.

The last speaker of this interesting stem cell session was Dr. Jane Visvader from the Walter & Eliza Hall Institute of Medical Research, Parkville, VIC, Australia, who delivered her lecture on the mammary epithelial hierarchy and its implications for breast cancer. She affirmed that elucidation of the epithelial hierarchy in the mammary gland is an important prerequisite in understanding which of these populations is predisposed to neoplasia. She stated that they have isolated discrete populations of mouse mammary epithelial cells on the basis of cell-surface markers and defined a population that expresses "basal" markers and is highly enriched for mammary stem cells. A luminal progenitor cell was prospectively isolated from the mouse mammary gland and shown to be differentially regulated by Notch 1 and GATA-3, which influenced luminal cell fate determination and differentiation, respectively. She acknowledged that these studies in mice have been extended to human breast tissue to define the cellular hierarchy and changes that it undergoes during neoplasia. She also declared that analogous to the mouse mammary gland, they have prospectively isolated three epithelial subpopulations: basal stem/progenitor cells identified by transplantation into "humanized" mammary fat pads, luminal progenitor and mature luminal cells. She concluded by saying that the luminal progenitor cell is a key target of transformation in *BRCA1* mutation carriers.

SESSION 2: PHOSPHATIDYLINOSITOL 3-KINASE SIGNALING

Dr. Ramon Parsons of the Columbia University Institute for Cancer Genetics, New York, NY, chaired this session after a coffee break, which included four interesting presentations on phosphatidylinositol 3-kinase (PI3K) signaling, including his own on the PTEN (phosphatase and tensin homolog) pathway in breast cancer. Dr. Parsons stated that PTEN is one of the most frequently altered tumor suppressors in human cancer. It is regulated by a number of mechanisms, some of which are co-opted during tumor development to reduce the level of functional PTEN in a tumor. He discussed recent developments in the identification of a protein, P-Rex2, which is able to inhibit PTEN phosphatase activity. He concluded his talk with an optimistic note, stating that understanding the mechanisms of PTEN regulation in cancer will hopefully be useful for designing strategies for inhibiting the PI3K pathway for therapeutic benefit in the near future.

Dr. William Muller of McGill University, Montreal, QC, Canada, delivered the next talk on the role of PI3K- and Akt-coupled signaling pathways in mammary development and tumorigenesis. Dr. Muller discussed that the PI3K/Akt survival pathway is often dysregulated in cancer and coexpression of activated c-AKT with activated erbB-2 or polyoma virus middle T antigen uncoupled from the PI3K pathway (PyVmTY315/322F) accelerates mammary tumor development but

cannot rescue the metastatic phenotype associated with these models. He concluded his presentation saying that the highly conserved kinases have distinct biological and biochemical outputs that play opposing roles in mammary tumor induction and metastasis. The mammary epithelial disruption of 14-3-3s resulted in a dramatic acceleration in tumor onset and plays a critical role in mammary tumor progression.

Dr. Pier Paolo Pandolfi of the Beth Israel Deaconess Cancer Center and Harvard Medical School, Boston, MA, delivered a talk on high-throughput screening (HTS) analysis of an miRNA protogenomic network that downregulates PTEN in cancer. Later, Dr. Levi Garraway of the Dana-Farber Cancer Institute, Boston, MA, delivered the last presentation of this session on some of the new insights into PI3K-directed signal transduction in breast cancer, which included a good amount of data from his own laboratories. As some of the work presented is to be published, he was cautious in giving more details.

SESSION 3: TRANSLATIONAL RESEARCH

Dr. Carlos Arteaga of the Vanderbilt-Ingram Cancer Center, Nashville, TN, acted as the chairperson of this post-lunch session on translational research, which included three invited lectures including his own presentation. Dr. Robert Kerbel of the Sunnybrook Health Sciences Center, Toronto, ON, Canada, delivered an invited talk on translational research studies of antiangiogenic therapy in the advanced metastatic and adjuvant breast cancer settings. A recurring and common criticism of preclinical experimental therapeutic studies in mice is their limited or even no predictive clinical value due to failure of the same or similar therapies when tested in subsequent clinical settings (5). He also addressed the new developments in his laboratory, where they have developed a series of highly metastatic variant sublines from human cancer cell lines, including the breast cancer line MDA-MB-231 (6-8). He also reported that they are developing new models of advanced metastatic disease like early-stage disease models, namely, postoperative adjuvant therapy of microscopic metastases. Later, Dr. Carlos Arteaga delivered an authoritative presentation on erbB-3 (HER3) and its role in erbB-2 (HER2)-mediated tumorigenesis and resistance to anti-HER2 drugs. Dr. Nancy Davidson of the University of Pittsburgh Cancer Institute, Pittsburgh, PA, delivered her presentation on epigenetics and breast cancer as the last lecture of this session. Dr. Neal Rosen from the Memorial-Sloan Kettering Cancer Center, New York, NY, was scheduled to deliver a lecture in this session but could not make it.

SPECIAL PRESENTATION: THE ARMY OF WOMEN (AOW)

The inclusion of a presentation by Dr. Susan Love of the Dr. Susan Love Research Foundation (DSLRF), Santa Monica, CA, on the concept and initiation of "The Army of Women (AOW)", detailing it as a new resource to accelerate research into the cause and prevention of breast cancer, really caught the attention of all (9). Dr. Love explained the history and aims of the DSLRF. The DSLRF and The Avon Foundation for Women jointly launched "The Love/Avon Army of Women" in October 2008 as an online recruitment resource designed to create an effective partnership between women and the research community in an effort to accelerate breast cancer research. An impressive number (over 300,000) of women have become AOW members voluntarily so far (in the span of just 1 year), and the growing participation of more women enthusiastically enrolling themselves online is proof of the success of this novel attempt. Members include women who have and have not been diagnosed with breast cancer, as well as those with and without a family history of breast cancer, age groups ranging from 18 to 100 years and representing all 50 states of the U.S. and 47 other countries. Dr. Love reported that over 12,000 AOW members have been participating in the research process and that this method of recruitment has been found to be both effective and efficient.

Dr. Love affirmed that AOW is a novel resource for breast cancer scientists to accelerate accrual, to expand the diversity of their subject population, to increase the number of subjects and statistical significance of their results. Moreover, they can obtain exactly the type of subjects/specimens they need when they need it. This new partnership between women and scientists can revolutionize research and accelerate efforts to eradicate breast cancer. The presentation was so effective and appealing that most of the women participants enrolled themselves soon after attending the lecture. Being the last lecture for the day's proceedings, there was much interaction between the speaker and the participants. The theme was quite novel and it certainly opened a new initiative in recruiting appropriate subjects for specific investigations.

SESSION 4: DETERMINANTS OF BREAST CANCER RISK (DAY 3)

Dr. David Hunter from Harvard University, Boston, MA, acted as a speaker as well as the chairperson for the session on determinants of breast cancer risk. He delivered an interesting opening lecture of the day on inherited susceptibility alleles, their discovery, biology and translation to risk prediction. His presentation included a good amount of the data from his own laboratories, as well as clinics. The next speaker of the session was Dr. Norman Boyd from the Ontario Cancer Institute, Toronto, ON, Canada, who spoke on mammographic density and breast tissue composition in young women. Dr. Boyd explained the theoretical Pike model of "breast tissue age", and empirical evidence indicates that the breast is especially susceptible to the effects of carcinogens at an early age and suggests that strategies to prevent breast cancer will be most effective if started early in life. He revealed his findings which showed variations in the percent mammographic density (PMD) to be associated with a large difference in the risk of breast cancer in women of middle age and older, to be highly heritable and strongly correlated with the water content of the breast, as assessed by magnetic resonance imaging (MRI). Dr. Boyd revealed that to date they have examined about 400 young women (aged 15-30 years) and their mothers. Breast MRI has been used to characterize breast tissue in all young women and a random sample of 100 mothers. Mean levels and variation in breast water content were greatest in young women aged 15-18 years, when susceptibility to carcinogens is also greatest. He also added that the breast water content in young women is correlated with their weight and height, suggesting that general measures of growth and development are associated with breast tissue composition. He also revealed that blood levels of growth hormone and sex hormone-binding globulin in all subjects, and in those aged 15-18 years estradiol, testosterone and progesterone, were associated with breast

water content. He indicated that both hormonal and genetic factors influence breast tissue composition in young women and presented many studies on a large number of twin (both female) subjects conducted in his laboratories. He further mentioned that studies to identify genetic determinants in the breast tissue composition of young women are in progress.

Dr. Thea Tlsty of the University of California School of Medicine, San Francisco, CA, delivered the last presentation of this session on early epigenetic and genetic events in carcinogenesis. Dr. Tlsty explained the major problems associated with the detection of cancers in the early stage rather than in the late stages of cancer progression (10). She maintained that failure in detecting cancer progression in the early stage could be due to the fact that the early lesions and transitions often occur 10-15 years prior to our ability to detect the disease by palpation or imaging (11, 12). By the time many cancers are detected, they have long since acquired the ability to generate micrometastases or populations of tumor cells that can develop drug resistance. Furthermore, the premalignant lesions are small, sporadic and arise in a nonsynchronized fashion, often making detection extremely difficult and analysis almost impossible. Dr. Tlsty revealed her findings that studies of human epithelial cells and fibroblasts from healthy individuals have been providing novel insights into how early epigenetic and genetic events affect genomic integrity and fuel carcinogenesis. Key epigenetic changes, such as the hypermethylation of the p16 promotor sequence, create a previously unappreciated preclonal phase of tumorigenesis in which a subpopulation of epithelial cells is positioned for progression to malignancy. These key changes generate epigenetic and genetic mosaicism, precede the clonal outgrowth of premalignant lesions and occur frequently in healthy, disease-free individuals.

SESSION 5: TUMOR MICROENVIRONMENT

Dr. Lisa Coussens from the Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, CA, was the chairperson for this session on tumor microenvironment and delivered the first lecture. Dr. Coussens delivered her talk on the regulation of protumor immunity and breast cancer development. She explained the clinical and experimental studies which established that chronic infiltration of neoplastic tissue by leukocytes, i.e., chronic inflammation, promotes the development and/or progression of various solid tumors; however, the organ-specific cellular and molecular programs that favor protumor as opposed to antitumor immunity by leukocytes are incompletely understood. She explained the role of leukocytes and B and T lymphocytes in breast cancer progression. She discussed the experimental studies which demonstrated that macrophages in primary mammary adenocarcinomas regulate a late-stage carcinogenesis by virtue of their proangiogenic properties, as well as fostering pulmonary metastasis by providing epidermal growth factor (EGF) to malignant mammary epithelial cells (MECs), thereby enhancing their invasive (and metastatic) behavior. She concluded her talk saying that when $CD4^+$ T lymphocytes are present in a T_H2-type tumor microenvironment, they can promote metastasis by regulating the protumor properties of tumor-associated macrophages (TAMs), as opposed to limiting or eradicating malignant cells by engaging cytotoxic mechanisms. This provocative realization provides a rationale for the development of anticancer therapeutics that neutralize the protumor properties of both adaptive and innate immune cells in the tumor microenvironment and periphery, which when delivered in combination with cytotoxic drugs or therapeutic bolstering antitumor immunity, may thereby extend the survival of breast cancer patients with advanced disease.

Dr. John Condeelis of the Albert Einstein College of Medicine, The Bronx, NY, presented his lecture on the molecular and cellular basis of the invasion and intravasation microenvironments in breast tumors. Dr. Condeelis explained the recent convergence of technologies for expression profiling and multiphoton-based intravital imaging (13). He explained how carcinoma cell behavior is profoundly influenced by microenvironments within the breast tumor, including chemotaxis to blood vessels and invasive migration with macrophages involving autocrine (human) and paracrine (mouse) interactions (14-16). He concluded his talk saying that the key genes in the invasion signature have been studied successfully in preclinical models for their ability to alter metastatic outcome. The invasion signature predicts metastatic outcome in breast cancer patients and has been used to develop several new prognostic markers that have been used successfully in clinical trials.

Dr. Pepper Schedin from the University of Colorado at Denver, Aurora, CO, delivered a lecture on mammary gland involution, microenvironment and tumor progression. Dr. Schedin explained the difficulties in detecting breast cancer in the early stage. She discussed pregnancy-associated breast cancer (PABC), which accounts for 45% of all breast cancers in young women and has significantly reduced 10-year survival rates compared with non-PABC. In rodent models, after parturition or lactation, a physiologically normal tissue remodeling program is activated that mimics wound healing and inflammation. Shared characteristics include deposition of fibrillar collagen, high matrix metalloproteinase MMP-2, -3 and -9 activity, release of bioactive fragments of collagen I, fibronectin, laminin 1 and laminin 5, increased cytokine levels, including MCP-1, IL-4, IL-13 and TGF-β, and infiltration of alternatively activated/M2 macrophages similar to immune suppressive tumor-associated macrophages. She revealed experimental findings which indicate the impact of involution on invasion and metastasis of PABC in the MCF-10DCIS human cell line in a murine xenograft model. She demonstrated results that post-partum mammary gland involution in women is characterized by a proinflammatory microenvironment, implicating physiological tissue inflammation in the poor prognosis of PABC, and is associated with increased tumor invasion and metastasis in a new murine model of PABC. Dr. Valerie Weaver of the University of California, San Francisco, CA, delivered a talk on mechanotransduction and tumor invasion.

SESSION 6: TUMOR DORMANCY AND METASTASIS

Dr. Lewis Chodosh of the University of Pennsylvania, Philadelphia, PA, was the chairperson for this post-lunch session on tumor dormancy and metastasis. Dr. Chodosh delivered the opening lecture of the session on targeting metastasis, tumor dormancy and recurrence for breast cancer therapy. He explained the recurrence of breast cancer and its causes. He also explained that in breast cancer, disseminated tumor cells are present in 20-40% of primary breast cancer patients lacking any clinical or histopathological signs of metastasis. These cells have the ability to survive in a presumably

dormant state within tissues for up to 20 years, either as solitary cells or as micrometastases. The residual cells re-emerge from this latent state and resume growth, leading to cancer recurrence. As such, metastasis, tumor dormancy and recurrence constitute fundamental manifestations of tumor progression, which is responsible for a vast majority of breast cancer deaths. He revealed experimental findings from his laboratories, where they have developed and validated a series of doxycycline-inducible transgenic mouse models for Myc-, HER2/NEU-, Wnt-1- and Akt-overexpressing breast cancers that display key features of human breast cancer progression, including metastasis, minimal residual disease, dormancy and recurrence. These models are being used to elucidate the molecular pathways and cellular processes that contribute to these aspects of breast cancer progression.

Dr. Yibin Kang from Princeton University, Princeton, NJ, presented his lecture on mechanistic insights of breast cancer metastasis from functional genomics. Dr. Kang gave an overview of major challenges in metastasis research to identify functionally important and clinically relevant mediators of metastasis among a myriad of genetic alterations that routinely occur in metastatic tumor cells. He explained how the application of genomic profiling technology in animal models of cancer metastasis and clinical tumor specimens has allowed the discovery of novel metastasis genes and the analysis of their functions at different stages of metastatic progression. He revealed several of their experimental findings on the genomic profiling of bone metastatic variants of the MDA-MB-231 breast cancer cell line to identify a panel of candidate bone metastasis genes, including two genes that encode MMP-1 and ADAMTS-1. Elevated levels of both MMP-1 and ADAMTS-1 were observed in a significant proportion of breast tumors and are strongly correlated with a higher risk of bone metastasis. Molecular targeting of MMP-1 and ADAMTS-1, combined with inhibition of EGFR, may potentially reduce the risk of bone metastasis for a significant number of breast cancer patients. The experimental findings from the genomic profiling of a mouse model of breast cancer dormancy and metastatic recurrence in bone discovered that vascular cell adhesion molecule V CAM-1 is essential for the conversion from dormancy to macrometastasis. He concluded that they designed and applied a novel computational algorithm to identify recurrent genomic alterations directly linked to altered gene expression in poor-prognosis breast tumor samples.

Dr. Klaus Pantel of the University Medical Center Hamburg-Eppendorg, Hamburg, Germany, delivered the next presentation on cancer micrometastasis. Dr. Pantel explained the deficiencies of detecting the early spread of tumor cells by current imaging technologies (17). He described two methods that are useful in patients with cancer and no signs of overt metastases, and how sensitive methods have been developed to detect circulating tumor cells (CTCs) in the peripheral blood and disseminated tumor cells (DTCs) in the bone marrow (18, 19). Monitoring of CTCs will provide new insights into the selection of tumor cells under biological therapies. Molecular characterization of DTCs and CTCs opens up a new avenue for understanding early metastatic spread of tumor cells and might contribute to the identification of MSCs with important implications for future therapies.

Dr. Christoph Klein of the University of Regensburg, Regensburg, Germany, delivered the last of the presentations of this session on the genomic analysis of disseminated breast cancer cells. Dr. Klein revealed his experimental findings and that his group has developed methods to characterize the genome and the transcription of single cells at high resolution. He also explained the requirement of new methods that directly characterize minimal residual cancer for patient stratification and selection of molecular targeted therapies.

SESSION 7: BASAL-LIKE BREAST CANCER (DAY 4)

Dr. Kornelia Polyak of the Dana-Farber Cancer Institute, Boston, MA, was the chairperson for this session on basal-like breast cancer. This was the final session of the conference, comprising four invited talks. Dr. Polyak delivered her opening lecture on basal-like breast cancer and the molecular determinants and new therapeutic targets. She discussed that the comprehensive gene expression profiling of human breast carcinomas revealed molecularly distinct subtypes with different clinical outcomes. Basal-like tumors are estrogen receptor $(ER)^-$, progesterone receptor $(PR)^-$ and $HER2^-$ and have a higher risk of developing distant metastases and a worse outcome. Presently, there is no specific therapy for basal-like breast tumors, because there is no known targetable molecular alteration present in these cells. She shared her experiences and experimental findings in characterizing the molecular profiles of stem cell-like ($CD44^+$) and more differentiated luminal epithelial ($CD24^+$) cells from breast carcinomas. Her group determined that even "luminal A" tumors have a subset of tumor cells that are $CD44^+/ER^-/PR^-/HER2^-$ stem cell-like and that distinct breast tumor subtypes have a varying number of more differentiated and stem cell-like cells within the tumors. Genes and signaling pathways identified in this study could potentially be candidates for novel therapeutic targets in breast cancer, especially in the basal-like subtype.

Dr. Jos Jonkers of The Netherlands Cancer Institute, Amsterdam, the Netherlands, delivered a lecture on targeting homologous recombination deficiency in conditional mouse models of BRCA-associated breast cancer (20). Dr. Jonkers explained about the genetically engineered mouse (GEM) models of human cancer and their significance to gain a detailed insight into the specific genetic changes that drive tumor initiation and progression, and which also provide the tools to define the underlying mechanisms of drug response and acquired resistance (21, 22). Dr. Andrea Richardson of Brigham and Women's Hospital, Boston, MA, delivered the next presentation on the pathology and molecular classification of basal-like breast cancer (23). Dr. Richardson given a detailed explanation of the classification of human tumors based on observed similarities and differences. The important features considered in tumor classification include the organ of origin (breast cancer vs. lung cancer), cell type (keratin-producing epithelial carcinomas vs. mesenchymal sarcomas) and functional characteristics (secretory "adenocarcinomas", stratified "squamous carcinomas" and contractile "myoepithelial carcinomas"). Most breast cancers are glandular adenocarcinomas, but rare breast sarcomas, myoepithelial carcinomas or squamous cell carcinomas can also occur (24, 25).

Dr. Alan Ashworth from the Institute of Cancer Research, London, U.K., delivered the last of the session lectures on the synthetic lethal approaches to the development of new therapies targeting DNA repair deficiencies in cancer. Dr. Ashworth presented in detail on tumors harboring defects in their ability to maintain genomic

integrity. This contributes to the mutational burden and likely fosters pathogenesis. He also explained the therapeutic strategies to exploit these defects using a synthetic lethal approach to target the defect in DNA repair by homologous recombination in tumors with a *BRCA1* or *BRCA2* mutation. This strategy using poly(ADP-ribose) polymerase (PARP) inhibitors showed considerable promise in the clinic. He concluded his talk saying that the synthetic lethal approach is also applicable to other cancer types.

POSTER SESSIONS

Poster presentations were divided into two sessions, with an allotted time span of 3 h each on the second and third days of the conference. Approximately 200 posters were presented in all, providing enough opportunity to all of the delegates to participate in detailed discussion and one-on-one interactions. Most of the posters were original contributions from different laboratories involved in cell biology, genetic technology and clinical applications of breast cancer research. They also included several posters from reputed industrial laboratories.

Mr. Marotta from the Dana-Farber Cancer Institute, Boston, MA, presented a poster on a lentiviral small hairpin RNA (shRNA) screen of cell type-specific genes which identifies novel targets for breast cancer therapy (26). His group has conducted an shRNA screen with infected breast cancer cell lines resembling $CD44^+$ or $CD24^+$ cells with lentiviruses carrying shRNAs targeting 1,576 genes. From these experiments, 15 genes were identified which are important for cell viability in basal-like (which are similar to $CD44^+$ cells) but not in luminal breast cancer cell lines (which are similar to $CD24^+$ cells). They identified the genes that are more highly expressed in $CD44^+$ cells compared to $CD24^+$ cells which are specifically required for basal-like breast cancer cell growth and survival and that could be targeted to treat aggressive basal-like breast cancer, as well as other breast tumor subtypes containing $CD44^+$ cells. These experiments will ultimately help in improving therapies for patients with breast cancer through the discovery of ways to specifically kill $CD44^+$ cells.

Mr. Curtis from the University of Cambridge, Cancer Research UK Cambridge Research Institute, Cambridge, U.K., presented a poster on the characterization of 1,000 breast cancer genomes and transcriptomes, explaining an integrated analysis of copy number, allelic ratios, loss of heterozygosity and gene expression for 1,000 primary tumors aimed at further characterizing the complex genomic and transcriptional landscape of breast cancer (27). High-density SNP-CGH arrays were employed to assay allele-specific and total copy number, as well as allelic imbalance on 1,001 fresh-frozen tumors. Matched RNA from 825 samples was hybridized to Illumina H12 arrays for gene expression analysis. For a subset of cases, conventional Sanger sequencing was performed to survey the mutational spectrum of *TP53*. Additional orthogonal data included key clinical covariates such as age of diagnosis, lymph node status, ER status, HER2 status, grade and stage.

Another poster from the Dana-Farber Cancer Institute by Mr. Choudhury demonstrated the work on pregnancy-induced molecular changes in the human mammary epithelium. Women who give birth in young adulthood exhibit a reduced lifetime risk of postmenopausal ER^+ breast cancer. Further multiple pregnancies enhance this protective effect, which might be due to epigenetic and gene expression changes induced in mammary epithelial progenitors (28). This hypothesis was tested by analyzing the gene expression and DNA and histone methylation profile of lin/$CD44^+$ mammary epithelial progenitors and $CD24^+$ differentiated luminal epithelial cells isolated from age- and ethnicity-matched parous and nulliparous women. These findings will not only improve the understanding of pregnancy-induced reduction of breast cancer risk, but the genes and pathways they identified can also potentially be used as biomarkers for risk prediction, as well as targets for chemopreventive approaches.

CONCLUSIONS

Overall, the conference evidenced the latest work on several focused aspects of breast cancer and provided good insight. In fact, two keynote addresses were scheduled in the scientific program, one at the beginning and the other at the end. Unfortunately, Prof. Joan Brugge of Harvard Medical School, Boston, MA, who was to speak on modeling epithelial morphogenesis in three dimensions, could not make it. Most of the speakers presented their original data and could authoritatively discuss and debate several issues.

Several interesting and significant findings were presented during the symposium. Some of the highlights are mentioned below. The development of a unique p53-null murine breast cancer model to distinguish a tumor-initiating subpopulation of cells from others by Dr. Rosen was one of them. The TICs expressed higher levels of DNA damage response genes and DNA repair genes. Dr. Visvader's isolation of a luminal progenitor cell from the mouse mammary gland, which was shown to be differentially regulated by Notch 1 and GATA-3, is an interesting finding. His group isolated three epithelial subpopulations: basal stem/progenitor cells identified by transplantation into "humanized" mammary fat pads, luminal progenitor and mature luminal cells. The luminal progenitor cell is a key target of transformation in *BRCA1* mutation carriers.

Dr. Kerbel's disclosure of the development of a series of highly metastatic variant sublines from human cancer cell lines, including the breast cancer line MDA-MB-231, was an interesting feature. Strategies to prevent breast cancer will be most effective if started early in life. The findings of Dr. Boyd showed variations in PMD to be associated with a large difference in the risk of breast cancer in women of middle age and older, to be highly heritable and strongly correlated with the water content of the breast, as assessed by MRI. Similarly, in the detection and diagnosis of breast cancer, Dr. Tlsty's findings related to studies of human epithelial cells and fibroblasts from healthy individuals provided novel insights into how early epigenetic and genetic events affect genomic integrity and fuel carcinogenesis. Dr. Schedin's discussion on PABC, which accounts for 45% of all breast cancers in young women and has significantly reduced 10-year survival rates compared with non-PABC, was also an important lecture.

Furthermore, Dr. Chodosh's findings on a series of doxycycline-inducible transgenic mouse models for Myc-, HER2/NEU-, Wnt-1- and Akt-overexpressing breast cancers that display key features of human breast cancer progression, including metastasis, minimal residual disease, dormancy and recurrence can open up a new area. The applications of genomic profiling technology in animal models of cancer metastasis and clinical tumor specimens has allowed the

discovery of novel metastasis genes and the analysis of their functions at different stages of metastatic progression.

One of the most impressive aspects of the conference was the encouragement and awards offered to young researchers (scientists in making). In a conference of this magnitude giving as many as 30 (Scholars in Training: 21; AACR Avon Foundation Awards: 8; and AACR Minority Scholar in Cancer Research Award: 1) travel awards is highly appreciable. Unlike other international meetings, the hospitality was also very impressive. The efforts made by the organizers, the AACR and more particularly the chairpersons, are highly appreciated, as they could selectively pick eminent workers in different fields of research in breast cancer and thus could make this conference interesting as well as informative.

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DISCLOSURES

The authors state no conflicts of interest.

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