Meeting report

93rd Annual Meeting of the American Association for Cancer Research, San Francisco, CA, USA, 6–10 April 2002

Virginia Novaro and Derek Radisky

Lawrence Berkeley National Laboratory, Berkeley, California, USA

Correspondence: Virginia Novaro, Lawrence Berkeley National Laboratory, 1 Cyclotron Road, MS 83-101, Berkeley, CA 94720, USA. Tel: +1 510 486 4368; fax: +1 510 486 5586; e-mail: vnovaro@lbl.gov

Received: 16 April 2002
Accepted: 30 April 2002
Published: 10 May 2002

Breast Cancer Res 2002, **4**:165-168

(Print ISSN 1465-5411; Online ISSN 1465-542X)

Introduction

The 93rd Annual Meeting of the American Association for Cancer Research (AACR) was held in the vast underground complex of the Moscone Convention Center in downtown San Francisco, through mostly beautiful early summer weather during 6–10 April 2002.

This diverse meeting, attended by more than 14,000 people, was dedicated to all methods of cancer research, from basic cell biology to advanced clinical trials. The meeting was presented in a multitude of formats: interactive 'meet the expert' sessions (at 07:00 a.m.!), plenary lectures, symposia, minisymposia, poster sessions, educational workshops, and panel discussions. Despite the scope of the meeting, many of the presentations had an intimate feel. This was in part because of the quantity and quality of not-yet-published data that was presented, and in part because of the atmosphere of discussion, even in the largest lecture halls.

The present report will cover many of the topics that were presented. Because of the scope of the conference, however, the summaries that follow are only a representative sampling.

Molecular profiling: cDNA arrays and proteomics

As evidenced by many talks at the conference, RNA transcript profiling technologies continue to mature, clearly benefiting from the completion of the human genome sequence. Kornelia Polyak (Dana-Farber Cancer Institute, Harvard University, Boston, MA, USA) described serial analysis of gene expression techniques used to identify genes preferentially expressed in ductal carcinoma *in situ*. Laura Van't Veer (The Netherlands Cancer Institute, Amsterdam, The Netherlands) performed a study in which cDNA was prepared from affected tissue from breast cancer patients, both before and after a 5-year treatment period. Transcript analysis revealed a characteristic gene expression pattern associated with intervening progression to metastasis. This pattern was used as a tool to evaluate a test group of patients and was found to have a better predictive value than existing methods.

The sophistication and utility of proteomic analyses have similarly grown. Several presentations came from the laboratory of Emmanuel Petricoin (National Institutes of Health, Bethesda, MD, USA), addressing the use of proteomics to dissect the breast cancer phenotype in the context of native cell–cell and cell–extracellular matrix interactions. To improve signal strength and to reduce background, human breast tumor cells were obtained by laser capture microdissection of tumor tissue samples or from nipple aspirate fluids, and were then subjected to western analysis, protein microarray, and surface-enhanced laser desorption/ionization–time of flight mass spectrometry. These techniques were used to compare normal breast epithelium and invasive carcinomas, both before and after therapy (e.g. Iressa inhibition of epidermal growth factor [EGF]/ErbB1 signaling, or herceptin inhibition of HER2/ErbB2 signaling). Similar work was presented by Jinong Li (Johns Hopkins, Baltimore, MD, USA), who

AACR = American Association for Cancer Research; EGF = epidermal growth factor; ER = estrogen receptor; MRI = magnetic resonance imaging; PCR = polymerase chain reaction.

analyzed surface-enhanced laser desorption/ionization–time of flight mass spectra of serum proteins to identify a molecular signature of breast cancer.

A yet more sophisticated approach to proteomic analysis was presented by Richard Caprioli (Vanderbilt University, Nashville, TN, USA), in which the related technique of matrix-assisted laser desorption/ionization–time of flight mass spectrometry was used to scan the sample, creating an image in which each pixel was composed of a complete mass spectrum (from 2 to 100 kDa). Scanning through the mass spectra revealed the distribution patterns of proteins for any given molecular weight, and the identity of the proteins could be pursued using mass spectrometry–mass spectrometry techniques. Caprioli is currently developing a microscopic laser with a resolution of 2 μm to be used for imaging subcellular structures. The tremendous size of his datasets points toward the greatest current challenge in this field: the development of more sophisticated computational tools to dissect key relevant markers.

Nuclear structure, chromatin dynamics, and genomic instability

In an early morning session, Stephen Doxsey (University of Massachusetts Medical School, Boston, MA, USA) presented an excellent review of centrosome function and key centrosome proteins, and gave a discussion of the role of centrosome defects in the generation of genetic instability and tumor progression. He also presented work from his laboratory towards understanding these phenomena.

Joe W Gray (University of California, San Francisco, CA, USA) presented a progression model that correlates the number of gene abnormalities and overall genomic instability with the grade of malignancy in breast tumor (from normal tissue, to hyperplastic lesions, to carcinoma *in situ*, to invasive and metastatic tumors). William R Sellers (Dana-Farber Cancer Institute, Boston, MA, USA) showed that receptor tyrosine kinase genes are a particular target of recurrent genomic aberrations during tumorigenic progression, an observation relevant to therapies targeting those receptors or their signaling mediators.

The role of BRCA1 as a tumor suppressor acting in DNA repair and the maintenance of genomic stability was addressed in presentations by Stephen C West (Imperial Cancer Research Fund, London, UK) and by David M Livingston (Dana-Farber Cancer Institute, Boston, MA, USA). The recently demonstrated interaction of BRCA1 with a variety of oncoproteins and tumor suppressors (e.g. BRCA2, *myc*, p53, BARDI, etc.) was cited as evidence of the complexity of BRCA1 signaling pathways. Results were presented that BRCA1 acted to integrate signals arising from the action of these other proteins. Furthermore, Livingston presented a hypothesis of why BRCA1 defects primarily manifest in women as breast cancer, when he showed that BRCA1 could influence X-chromosome localization and inactivation.

Another alternative theory of breast cancer etiology was presented by James F Holland (Mt Sinai School of Medicine, New York, NY, USA), who proposed the existence of a human-infectious form of the mouse mammary tumor virus. Furthermore, he suggested that this virus could be responsible for a substantial number of breast cancers, such that the different distribution of mouse species between Asian and non-Asian countries could account for the different risks of breast cancer between Asian and non-Asian women.

Targeting signaling pathways

The Dorothy P Landon/AACR prize for translational research was given both to Elwood V Jensen (University of Cincinnati, Cincinnati, OH, USA), who presented a historical synopsis of the identification of the estrogen receptor (ER), and to V Craig Jordan (Northwestern University, Chicago, IL, USA), who summarized the clinical potential of anti-estrogens such as tamoxifen and raloxifene in the treatment of breast cancer.

Continuing the theme of exploring the mechanistic basis of signaling pathway inhibitors, Myles Brown (Dana-Farber Cancer Institute, Harvard University, Boston, MA, USA) discussed how the tissue-specific effects of tamoxifen can be dissected with chromatin immunoprecipitation experiments, and how these results can point towards yet more efficient chemoprevention strategies. This was followed by a presentation from Carlos Arteaga (Vanderbilt University, Nashville, TN, USA), speaking about successes with pathway inhibitors such as herceptin, which inhibits HER2/ErbB2, and Iressa, which inhibits EGF receptor/ErbB1, and how these agents can have synergistic effects. A warning against simplistic approaches with these inhibitors as treatments for breast cancer was given by David F Stern (Yale University School of Medicine, New Haven, CT, USA), who discussed the complexity and heterogeneity in mechanisms of HER2/ErbB2 activation and the fact that different agonists can lead to completely different transcriptional responses, such that herceptin may be an effective treatment for a subset of, but not all, HER2/ErbB2 overexpressing tumors. In relation to this, Stern warned of the potential problem of using receptor levels as a sole prognostic indicator, and suggested that phosphorylation-specific antibodies to detect ErbB2 activation could be more reliable.

Leena A Hilakivi-Clarke (Georgetown University, Washington, DC, USA) spoke of her theory that the estrogen effect in breast cancer occurs through the influence of estrogen on a preinitiation step, rather than at initiation or progression. Namely, that estrogen acts as a carcinogen (or as a

potentiator of carcinogenesis) during the fetal through early developmental periods, but acts in suppressing preinitiation events during puberty and pregnancy. Hilakivi-Clarke hypothesized that this effect could be due to the property of estrogen to upregulate expression and activity of BRCA1. To apply this theory towards practical treatments (since it is not reasonable to give estrogen supplements to prepubescent girls), she has been experimenting with dietary treatments that affect circulating estrogen levels or activity, and assaying the results in the rat breast cancer model.

Many general presentations contained many principles that apply to breast cancer development and treatment. Frank McCormick (University of California, San Francisco, CA, USA) used his Memorial Award Lecture to provide an overview of the role of phosphatidyl-3-kinase, Ras, retinoblastoma, and p53 signal transduction pathways in normal cellular function and in carcinogenesis, with an aim towards developing integrative approaches that could lead to new therapies. Daniel D Von Hoff (Arizona Cancer Center, Tucson, AZ, USA) presented the results of a series of new anticancer agents used in clinical trials against breast and other cancers (full details are available online: http://www.azcc.arizona.edu/VonHoff).

Various symposia examined growth factor receptors as therapeutic targets, as well as how these strategies could be combined with other treatments. Considering the ErbB family, John Mendelson (University of Texas MD Anderson Cancer Center, Houston, TX, USA) discussed the two most promising new approaches: the use of function-blocking monoclonal antibodies (such as herceptin), and inhibitors of receptor tyrosine kinases (such as Iressa). The discussion showed that either treatment can result in inhibition of cell growth, in increased apoptosis, and in potentiation of tumor responsiveness to conventional cytotoxic chemical and radiation therapies. J Shou (Baylor College of Medicine, Houston, TX, USA) found that Iressa blocks crosstalk between the ER and EGF, and thus circumvents the acquired resistance to tamoxifen in breast cancer cells. R Bianco (Universita di Napoli 'Federico II', Naples, Italy) determined that the antitumor effect of ionizing radiation was potentiated by Iressa in diverse cancer cell lines. Santiago Ropero (Hospital 12 de Octubre, Madrid, Spain) showed, however, that combination treatment of breast cancer cells with herceptin and tamoxifen could be additive, synergistic, or antagonistic for cell growth, depending on concentrations and timing.

The advantages of the use of raloxifene over tamoxifen to reduce breast cancer risk were presented by Powel Brown (Baylor College of Medicine, Houston, TX, USA). Diverse clinical trials have shown these to include reduced risk of endometrial cancer. Brown also reviewed preclinical data of new agents (retinoids and cyclooxygenase-2 inhibitors) that prevent development of ER-negative and hormone-independent breast tumors. Many posters were related to the mechanisms involved in the development of ER-negative breast cancer. One such poster was by Jamie N Holloway (Lombardi Cancer Center, Washington, DC, USA), proposing that a substrate of MAP kinase is responsible for ERα downregulation and progression to a hormone-independent breast cancer. The poster by Yayun Liang (Medical College of Georgia, Augusta, GA, USA) described the antitumor effect of the antiprogestin mifepristone towards inhibiting cellular growth and inducing apoptosis in ERα-negative human breast cancer cells through a mechanism involving transforming growth factor beta 1.

Epigenetic contributions to breast cancer development

Rudolf Jaenisch (The Whitehead Institute for Biomedical Research, Cambridge, MA, USA) presented an overview of the epigenome and some of his recent research. While the best-characterized epigenetic mechanism involves DNA methylation of gene promoter regions, Jaenisch used colon and intestinal cancer models to show how additional epigenetic agents as diverse as DNA methyl transferases, histone deacetylases, histone acetyltransferases, transcription factors, and chromatin remodeling machinery can inhibit the expression of endogenous tumor suppressors.

Peter A Jones (USC/Norris Comprehensive Cancer Center, Los Angeles, CA, USA) reviewed evidence that aberrant methylation patterns are one of the most diagnostic and earliest features in cell transformation, and presented his own work employing a methylation-sensitive PCR technique to scan the genome in a bladder tumorigenic cell line. He provided direct evidence that the extensive *de novo* methylation of CpG islands in transformed cell promoter regions can effectively ensure the silencing of tumor suppressor genes. This was followed by a discussion of the practical uses of demethylating agents (5-aza-2′-deoxycytidine, or zebularine) to restore cellular growth control.

Thea Tlsty (University of California, San Francisco, CA, USA) has found epigenetic downmodulation by hypermethylation of the $p16^{INK4a}$ promoter in cancerous and precancerous lesions in many organs, including the breast, as well as in histologically normal breast tissue obtained by reduction mammoplasty. She showed that mammary epithelial cells with a methylated p16 promoter escape senescence, and that these cells pre-exist *in vivo* and also can be derived *in vitro*, and can bypass normal growth barriers by a cell intrinsic mechanism, in the absence of any external carcinogen. Tlsty proposed that these mammary epithelial cells could represent a breast cancer precursor, and she is currently trying to identify agents that selectively kill them while leaving normal mammary epithelial cells intact.

Integrative and complementary approaches

Ellen Warner (Toronto-Sunnybrook Cancer Center, Toronto, Ontario, Canada) described a study testing magnetic resonance imaging (MRI) and ultrasound techniques as additional/alternative methods for surveillance of women at high risk for breast cancer. The use of these techniques was prompted by the discomfort caused by conventional mammography, by the propensity of such cancers to develop in the dense breast tissue of younger women, and by the concern that the ionizing radiation associated with mammography could be deleterious for individuals defective in DNA repair pathways involving BRCA1 or BRCA2. MRI proved the most reliable method for early detection, identifying 13 out of 18 tumors. On combination of MRI with ultrasound and mammography, 17 of the 18 tumors were identified.

An excellent review of the current knowledge and challenges in the field of microenvironmental (cell–cell and cell–extracellular matrix) control of cellular proliferation was presented by Richard Assoian (University of Pennsylvania, Pittsburgh, PA, USA) in a 'meet the expert' sunrise session. The lively discussion far outlasted the scheduled length of the seminar. William S Dalton (University of Arizona, Tucson, AZ, USA), using a hematopoietic cell model, demonstrated the contribution of the tumor microenvironment on drug permeability and response, and ultimate tumor treatment or resistance. Dalton suggested that inhibition of cell adhesion or associated signaling pathways could be used as a mechanism for increasing the therapeutic effect of diverse chemotherapies.

Another new concept in drug resistance was presented by Luisa Iruela-Arispe (University of California, Los Angeles, CA, USA), who proposed that mammary tumors could be inhibited, even in the presence of activating oncogenes, by increasing the endogenous levels of anti-angiogenic factors. Michael S O'Reilly (University of Texas MD Anderson Cancer Center, Houston, TX, USA), a forum moderator of an angiogenesis symposium, presented the advantages and limitations of the clinical use of anti-angiogenic drugs in different types of cancer, concluding that anti-angiogenic drugs are significantly effective in combination with other therapies.

The 2001–2002 AACR President, Waun Ki Hong (University of Texas MD Anderson Cancer Center, Houston, TX, USA), presented an outstanding lecture concerning the necessity of integrating biological markers from target tissues with genetic susceptibility and epidemiologic studies to establish strategies for early cancer detection and chemoprevention. Hong proposed that cancer should be considered as a chronic disease that follows a dynamic process from initiation to progression, and he reviewed the most promising therapeutic targets in diverse cancers: inhibitors of growth factors, cyclooxygenase-2, angiogenesis, signal transduction pathways, and activators of apoptosis and differentiation.

A poster presented by Thorarinn Gudjonsson (The Panum Institute, Copenhagen, Denmark) described the isolation and immortalization of a human breast epithelial cell population with stem-like properties. These cells differentiate into myoepithelial and luminal epithelial-type cells on culture dishes, while they develop into gland-like structures with ducts and branching lobules when grown in three-dimensional matrices. While much more validation will be needed, the potential implications of this work to advance our understanding of the genesis of breast cancer were astounding.

Finally, in a very exciting ending for this intense meeting, Malcolm Brenner (Baylor College of Medicine, Houston, TX, USA) chaired one of the final symposia, concerning new therapeutic approaches using current advances in gene therapy. Many strategies were reviewed, including the design of specific molecular antibodies, the introduction of an oncolytic virus or specific vectors to correct tumor genetic defects, and genetic techniques to increase host resistance and/or tumor sensitivity to treatment. Similar techniques may ultimately lead to increased effectiveness of endogenous antitumor immune responses.

Conclusion

The 93rd Annual Meeting of the AACR presented a wealth of data and ideas, and provided opportunities for interaction with the full spectrum of cancer researchers, from basic scientists to active clinicians. The primary frustration of the conference was the impossibility of attending every promising talk; even working together, we were unable to cover as much as we would have preferred. However, and perhaps because of this, conference abstracts and a number of the presentations are available online at the AACR web page (www.aacr.org). Furthermore, stories of general highlights are available to BioMedNet members (news.bmn.com/conferences).

The 94th Annual AACR conference will be held in Toronto, Ontario, Canada, 5–9 April 2003.