Breast Cancer Research and Treatment (2005) 90: 1–3 

*Statement*

# Consensus statement: Expedition Inspiration 2004 Breast Cancer Symposium 'Breast Cancer – the Development and Validation of New Therapeutics'

Marc E. Lippman[1], Chris Benz[2], Arul Chinnaiyan[3], David Flockhart[4], Adrian Harris[5], Clifford Hudis[6], C. Kent Osborne[7], Michael F. Press[8], James Rae[9], George W. Sledge[10], Laura Van 't Veer[11], and Max Wicha[12]

[1]*Department of Internal Medicine, University of Michigan Health System, Ann Arbor, MI;* [2]*Program of Cancer and Developmental Therapeutics, Buck Institute for Age Research, Novato, CA;* [3]*Department of Pathology, University of Michigan Health System, M4237 Medical Science I, Ann Arbor, MI;* [4]*Department of Medicine, Indiana University Cancer Center, Indianapolis, IN;* [5]*Cancer Research UK, Medical Oncology Unit, University of Oxford, Weatherall Institute of Molecular Medicine, John Radcliffe Hospital, Oxford;* [6]*Breast Cancer Medicine Service, Memorial Sloan-Kettering Cancer Center, New York, NY;* [7]*Baylor College of Medicine, Houston, TX;* [8]*USC Norris Comprehensive Cancer Center, Los Angeles, CA;* [9]*University of Michigan Health System, 4323 Medical Science I, Ann Arbor, MI;* [10]*Indiana University Cancer Center, Indiana Cancer Pavilion, Indianapolis, IN, USA;* [11]*Department of Pathology, The Netherlands Cancer Institute, Amsterdam, The Netherlands;* [12]*University of Michigan Health System, Ann Arbor, MI, USA*

## Introduction

The 2004 Expedition Inspiration Symposium was held February 2004 in Sun Valley, Idaho and entitled 'Breast Cancer – The Development and Validation of New Therapeutics'. In this consensus statement we will summarize some of the key issues which we believe have an impact on the rate of delivery of new therapeutics to the clinic.

This summary will be in three parts: a brief overview of the meeting, a discussion of issues which impact generally on the development of new therapeutics for cancer and finally detailed abstracts of the meeting with key references on the subject matter of each. By way of introduction it is worth pointing out that the pace of basic and translational research underpinning new clinical initiatives is astounding. New technologies, new targets and new drugs are being developed at an ever increasing rate. At the same time the incidence and prevalence of breast cancer both continue to increase internationally. It is therefore all the more critical to see that every possible avenue to accelerate the pace at which this science can be reduced to practice is pursued. This was the paramount goal at the meeting.

## Overview of the meeting

Laura Van't Veer, PhD opened the meeting with an update of the prognostic index that Netherlands Cancer Institute has developed using micro array profiling based on an analysis of thousands of expressed genes. They have been able to identify and categorize patients who appear either at sufficiently low risk of relapse to forego further therapy or to be at relatively higher risk of relapse (though not necessarily certain to benefit from more aggressive therapy). This is now being prospectively explored in two European trials.

Arul Chinnaiyan, MD, PhD, of the University of Michigan presented data on 'oncomine.org' a tool which he and colleagues have developed to provide the basis for meta-analyses of micro array studies. This versatile tool permits multiple comparisons amongst published studies including 'gene' (one gene many data sets) 'study' (one data set many genes). This provides a unique platform for cross validation across competing analytic platforms and the potential to develop even more discriminative gene sets for patient sub setting.

Kent Osborne, MD, of Baylor Breast Center focused his talk on the diverse pathways by which estrogens acting on estrogen receptors can affect tumor growth. The increasing complexity of this system involving (at least) two receptor genes, new multiple sites of cellular localization, has created a myriad of new potential sites for therapeutic modulation. This is further complicated by an expanding group of ligands with differing specificites as well as a plastic milieu of co-activators and repressors.

James Rae, PhD of the University of Michigan and David Flockhart, MD, PhD of Indiana University reviewed the complexity posed to therapeutics by the rapidly expanding field of pharmacogenomics. Eighty five percentage of all drugs including most therapies used for breast cancer require metabolic activation of metabolism which is regulated by enzymes which are variable in their activity. This variability is largely controlled by inheritance of expressed allelles of differing functionality. Drugs such as SERM's, taxanes and antimetabolites are profoundly affected by these pathways and furthermore there is considerable opportunity for induction (or repression) of metabolic activity by co-administered substances such as glucocorticoids.

Max Wicha, MD of the University of Michigan presented updated information on his long-standing collaboration with Michael Clarke, MD and other colleagues in which they have succeeded in identifying a miniscule sub population of cells from both normal and malignant breast tissue which appear to meet criteria for stem cells in that they have asymmetric mitosis giving rise to progenitor cells as well as more differentiated cell populations. The obvious implication of this work is that therapies which effectively treat the majority of tumor cells but 'miss' the stem cell population will fail while therapies directed at stem cells can potentially eradicate tumors. A corollary is that if stem cells are <1% of tumors then array analyses, etc. may fail to reveal properties of the most critical cells making up a cancer.

George Sledge, Jr, MD also from the University of Indiana, reviewed current progress in anti angiogenic approaches particularly those directed against VEGF. These clinical trials clearly requires better intermediate end points to monitor effects of novel agents on either vasculogenesis or blood flow. The redundancy of angiogenic mechanisms may imply that such therapies will have to be used at earlier points in tumor therapy – a goal of the current trial of beracizamab and taxol in metastatic breast cancer is now nearing its accrual target.

Michael Press, MND, PhD of USC Norris Comprehensive Cancer Center reviewed results of trastuzumab trials with a particular emphasis on the absolutely essential need to adequately quantify HER-2/neu over expression. There is clearly a substantial under estimation of effectiveness of trastuzumab therapy because many patients have been mis classified as over expressers on the basis of incorrect immuno histochemical assays. Best use of targeted therapies will obviously require accurate identification of the target plus evidence for modulation of the target by the therapeutic.

Clifford Hudis, MD of Memorial Sloan-Kettering Cancer Center reviewed the biologic basis that cyclooxygenase – 2 (cox-2) plays a role in human tumor progression. These studies have provided a basis for clinical trials of potent cox-2 inhibitors such as celecoxib. Because there are data that patients who over express HER-2/neu also over express cox-2, he outlined a trial in which patients whose tumors progress on trastuzumab with or without chemotherapy continued on that therapy but had celecoxib added to the regime. This study was negative but because the data with aromatase inhibitors in HER-2/neu over expressors appear so compelling, MA-27 C the intergroup trial comparing exemestane to anastrozole has a follow on randomization after 5 years to 3 more years of celecoxib versus placebo. He also raised the interesting notion with so many people on cox-2 inhibitors for non-malignant disease that a massive public health experiment may be underway testing the role of cox-2 in malignant progression.

Chris Benz, MD of the Buck Institute for Age Research spoke about the potential role of proteasomal degradation and inhibitors of this pathway as potential targets for breast cancer therapy. Using an NCI library of compounds with a substantial degree of structural diversity, he was able to identify both a proteasome inhibitor and a histone deacetylase inhibitor which were able to turn off the HER2 promoter and by this means lower expression of HER2/neu. These studies are early but may lead to novel approaches to targeting HER2-positive breast cancers.

Adrian Harris, MD, PhD from Oxford, England discussed pharmacodynamic end points for phase I/II trials. He raised the very interesting issue that response rates even for established agents may appear to be unacceptably low, by failing to interact with the target. He explored topoisomerase IIα which is the target of epipodophyllotoxin (VP-16) and showed that there was a remarkable variation in response rate of patients based upon expression of the target. Similarly, he presented data on COMET assays for DNA strand breaks, as well as assays of other control points for metalloproteinase inhibitors and anti angiogenic agents. All of these data have as their unifying principle the notion that it is critical to measure surrogate endpoints and validate that the therapeutic approach being attempted is interacting with the target.

Finally, Marc Lippman, MD of the University of Michigan presented data on new small molecule inhibitors of apoptosis. A near universal property of breast cancer is the over expression of anti-apoptotic molecules such as BCL-2 and BCL-$X_L$. Together with his collaborators they have identified several small molecules which can block the hetero dimerization of pro-apoptotic molecules such as BAX or BAD with BCL- or BCL- $X_L$. By blocking this hetero dimerization breast cancer cells appear to be sensitized to chemotherapeutic agents and radiation treatment. One of these molecules will soon be entering clinical trials.

## Consensus issues

A series of issues were discussed which were felt to have a substantial impact on the rapidity with which many new therapeutic approaches could be brought to clinical reality. Many of these issues could potentially be addressed and could result in speedier development of new therapeutics.

Slow accrual to and diminishing support for clinical trials has been a major impediment to the direct development of new therapeutics. In Great Britain, the National Health Service developed resources for supporting a network of clinical trials which led from a 2% to a 10% rate of accrual of patients with breast cancer on to clinical trials. In the United States funding to the cooperative groups has remained flat and cancer centers haven't sufficient resources to independently support the infrastructure necessary to conduct clinical

trials. In addition, there have been substantial issues with providing support for correlative studies of science. As a result, many agents are not being developed as effectively because of the failure to concurrently study target validation. In fact, the FDA has not supported target-based protocols as compared with disease-based trials. Clearly there is need for a new paradigm in which both industry and the FDA need to consider processes by which drug trials aimed at specific targets can be explored across disease types. In real dollars support for clinical trials has, therefore, declined as a result of inflation. Similarly, because of many bureaucratic issues in handling multiple IRB's and approval processes, many pharmaceutical companies have taken drug trials off-shore. An overhaul of IRB mechanisms is long overdue.

Yet another presumably inadvertent outcome of the Health Insurance Portability and Accountability Act (HIPAA) has been the very great difficulty of not only retrospective analyses of tumors but also prospective analyses. The combination of HIPAA and IRB regulations has crippled research on correlative science. Given the widespread ability now to perform both protein and RNA analyses on both previous frozen and paraffin embedded materials it is exceedingly unfortunate that much of this material remains un-explored in clinical trials because of the inability to obtain appropriate consents. Re-interpretation or re-writing of this legislation is required to assure adequate clinical materials for retrospective analysis whilst assuring appropriate patient confidentiality.

Over and over again we have seen agents with remarkable pre-clinical potency fail in the clinic because of apparently inadequate response rates. However, it should be recalled that were trastuzumab to have been used in un-selected breast cancer patients the response rates would have been 5% or less. Therefore there is a critical need for appropriate validation of targets. Clearly the drug must have a specific molecular target. That target must be measurable in a clinically relevant situation. The target must be biologically important and finally it must be modulated by the therapy resulting in clinical benefit.

For all these reasons and more, participants in the symposium developed a series of recommendations which we believe are worth significant discussion.

(I) Correlative studies accompanying large scale trials of biological agents should be strongly encouraged. At the FDA level, registration trials should potentially require prospective selection of relevant clinical materials for correlative studies which should be made available for independent investigators. There should be agreement on appropriate consent forms at the time of surgery which can allow clinical and biological information to be harvested in such a fashion so as to protect patient privacy, but none the less allow appropriate correlative studies to be done at a later time. Funds should be supplied to the cooperative groups so that appropriate correlative sciences studies can accompany clinical trials in an efficient manner.

(II) IRB mechanisms need to be reformed potentially at a national level. The processes of redundant bureaucratic issues have become so burdensome that clinicians are discouraged from participating in clinical trials. Pharmaceutical companies are discouraged from pursuing these trials. Academic teaching centers and clinical research in general is being slowed. Attention needs to be given at the national level to reform this process to not only insure continued patient safety, but to provide efficient mechanisms whereby trials can be proposed and incorporated into the clinical management plans at multiple centers.

(III) It is clear that the protection of intellectual property has inhibited both academic and industrial development of agents. Individual academic institutions rarely have the technical expertise to rapidly develop, protect, and license intellectual property. One possibility is to consider a multi-institution consortium to both protect intellectual property and do drug development. By adding value to potential therapeutics by bringing them to clinical trial substantial value can be added and this could potentially speed up drug development. At the present time there appear to be few federal mechanisms for funding this kind of drug development as the RO1 mechanism is both cumbersome and rarely suitable for research which is somewhat less hypothesis-driven.

(IV) Additional funding is needed to provide for research aimed at developing better methods for validating molecular targets and the interaction of drugs with those targets. There has been minimal cross-platform validation of technologies and unfortunately almost no effort to fund tumor acquisition fixation or storage such that materials can be used at a later date for multiple institutions.

*Address for offprints and correspondence:* Marc E. Lippman, MD, Department of Internal Medicine, University of Michigan Health System, 3101 Taubman Center, 1500 East Medical Center Drive, Ann Arbor, MI 48109-0368, USA; *Tel.*: +1-734-936-4495; *Fax*: +1-734-615-2645; *E-mail*: lippmanm@umich.edu