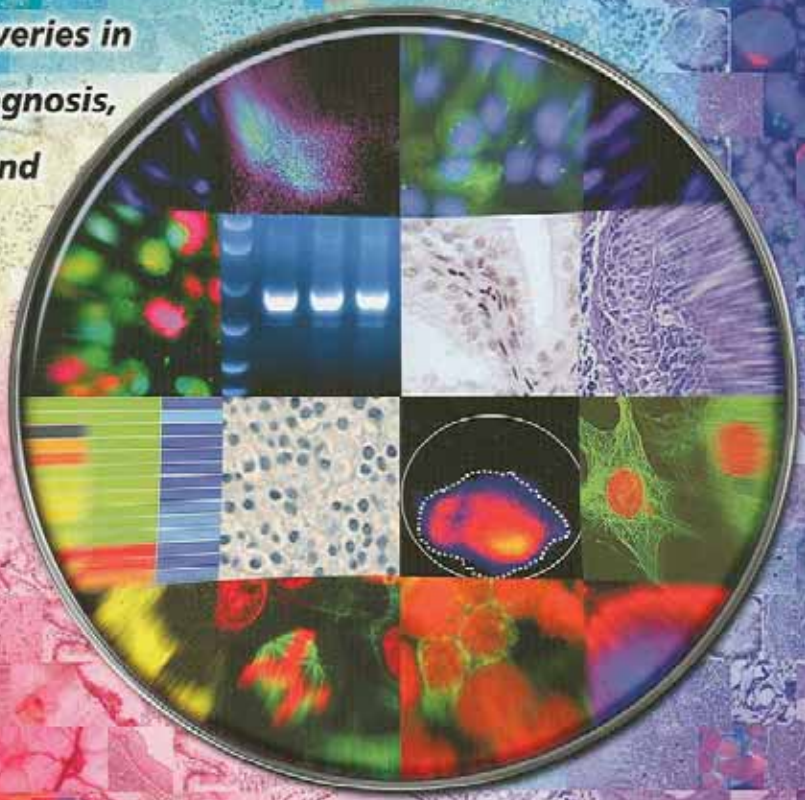
AACR American Association for Cancer Research

Featuring the Latest Discoveries in Etiology, Diagnosis, Treatment, and Prevention



96th Annual Meeting 2005

CME jointly sponsored by the University of Minnesota and the American Association for Cancer Research

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Proceedings Supplement

96th Annual Meeting
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American Association for Cancer Research

This volume contains abstracts that were accepted for presentation in the Late-Breaking Research Sessions. Abstracts are numbered from LB-1 through LB-322; however, several numbers may be omitted in the sequence. Abstracts were received directly from the authors by electronic submission. Every effort has been made to reproduce the content of the abstracts according to the electronic version submitted, except in certain instances where changes were made to comply with AACR style. The AACR does not assume any responsibility for proofreading or correcting any scientific, grammatical, or typographical errors, nor does the AACR assume responsibility for errors in the conversion of customized software, newly released software, or special characters. No responsibility is assumed by the AACR, publisher and copyright owner of the Proceedings Supplement; by the University of Minnesota; by Database Publishing Group, providers of abstract management software and services; or by the meeting organizers for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or for any use or operation of any methods, products, instructions, or ideas contained in the material herein. Independent verification of diagnoses and drug dosages should be made by readers or users of this information.

Continuing Medical Education (CME) Information

Accreditation Statement
This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the University of Minnesota and the American Association for Cancer Research (AACR). The University of Minnesota is accredited by the ACCME to provide continuing medical education activities for physicians.

Credit Designation Statement
The University of Minnesota designates this educational activity for a maximum of 51 Category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

Statement of Educational Need, Target Audience, and Learning Objectives
New technology and the resulting explosion in biological information have led to a significantly improved understanding of cancer development and progression, with major implications for cancer prevention, diagnosis, and treatment. By participating in the AACR 96th Annual Meeting, clinical investigators and physicians will better understand the contributions of laboratory research to patient care, the design and conduct of clinical research protocols, the epidemiological implications of cancer incidence, and the translation of the findings of laboratory research immediately for the benefit and care of the cancer patient. Through this participation of clinical investigators and physicians, laboratory researchers will obtain a better understanding of the wider context of their research and of the particular clinical problems that regularly confront physicians. This activity is presented for scientists and clinicians engaged in all aspects of clinical investigations pertaining to human cancer as well as the scientific disciplines of cellular and molecular biology; tumor biology; carcinogenesis; chemistry; clinical research; endocrinology; epidemiology; experimental and molecular therapeutics; immunology; and prevention research. At the conclusion of this educational activity, each participant should be able to:

- Understand the latest research findings in all areas of cancer research;
- Understand the importance of integrating information from basic and clinical research to conquer cancer;
- Understand the epidemiological implications of cancer incidence;
- Understand how technological advances can be used to accelerate discovery; and
- Use these findings to expedite the development of detection, prevention; and treatment strategies to reduce cancer incidence and mortality.

Disclosure Statement
It is the policy of University of Minnesota that the information presented at University of Minnesota-sponsored CME activities will be unbiased and based on scientific evidence. To help participants make judgments about the presence of bias, the University of Minnesota and the AACR provide information that speakers have disclosed about financial relationships they have with commercial entities that produce or market products or services related to the content of this CME activity. This disclosure information is available in the back of the Proceedings of the AACR. Disclosures received after the Proceedings went to press are listed in the back of this publication.

Claiming Credit
Individuals wishing to receive Category 1 credit for their attendance at this meeting should obtain a Documentation of Attendance and Request for Credit form from the CME booth located in the registration area. This form must be completed and returned to the CME booth to obtain a Certificate of Attendance.

Acknowledgment of Commercial Support
Commercial entities that provide unrestricted educational grants in support of this educational activity will be listed in the Annual Meeting Program.

Next Annual Meeting: April 1-5, 2006, Washington, DC

DNA from a few nanograms of DNA following a simple lysis (frozen tissue) or extraction (FFPE) procedure and that the DNA is suitable for use in genetic analysis applications.

LB-61 Comparison of mRNA and protein expression profiles between head and neck squamous carcinoma CAL27 and a daughter cell line expressing a dominant negative mutant IκBα by cDNA microarray and isotope-capture-affinity-tag (ICAT) analysis. Ming Yu, Xinping Yang, Ming Zhou, David A. Lucas, Thomas P. Conrads, Timothy D. Veenstra, Carter van Waes. NIH-NIDCD, Bethesda, MD, Tumor Biology Section, Head and Neck Surgery Branch, NIDCD, NIH, Bethesda, MD, NCI-Frederick, Frederick, MD.

Cal27 is an established cancer cell line derived from a head and neck squamous carcinoma (HNSCC). This tumor cell line is tumorigenic in nude mice and has been shown to be resistant to a variety of chemotherapeutic reagents, including 5-Fluourouacil (5-FU), which are used to treat HNSCC. We have found that this cell line exhibits constitutive NF-κB DNA binding and Luciferase reporter activity. B6-5, a Cal27 clone stably transfected with a dominant negative IκBα, showed two-fold increase over baseline IκBα protein level, and 75% decrease of NF-κB Luciferase activity compared to parent Cal27 cells. The IC50 of the IχBα transfectants to 5-FU is 1,000-fold less comparing to that of their parental cells, Cal27. To understand the underlying mechanism of the changes in these cells, we performed parallel studies to compare the expression levels of both proteins and mRNAs in these cells by applying ICAT and cDNA-Microarray analysis. ICAT analysis demonstrated decreased protein level of src and significant changes in myc and N-myc regulated proteins in B6-5 cells compared to Cal27. ICAT analysis also showed significant differences of proteins that are involved in cell cycle regulation, cell signaling pathways, including integrins, G proteins, ras related signaling pathways, RNA post-transcription modification, protein synthesis and metabolic processes related to glucose, fatty acids, amino acids, and nucleic acids. Western blot analysis confirmed the decrease at protein level of src and N-myc in B6-5 cells. Additionally, src protein phosphorylation status at Tyr 527 and Tyr-416 were decreased in B6-5 cells compared to Cal27 cells. cDNA microarray analysis of mRNA levels in these cells indicates decreased mRNA levels that are involved in cell cycle G2/M transition and mRNA levels of growth regulation in B6-5 cells. On the other hand, mRNAs that are involved in negative regulation of cell growth are increased in B6-5 cells compared to Cal27 cells. These data suggest that growth regulation in these cells has been changed. As myc can be regulated by NF-κB, by integrating these results from ICAT and cDNA-microarray analysis, we propose a hypothetical model regarding effects on inhibition of NF-κB on expression and the malignant phenotype. The study that we are presenting here is the first attempt to reveal the regulatory function of NF-κB by incorporating expression levels of protein with that of mRNA in Head and Neck cancer cells.

LB-62 Can computational structural biology be of help in rationalizing clinical data? The Abl/imatinib paradigm. Sabrina Pricl, Elena Tamborini, Marco Ferrone, Maria Silvia Paneni, Maurizio Fermeglia, Marco A. Pierotti, Silvana Pilotti. University of Trieste, Trieste, Italy and Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy.

Background: Several Bcr-Abl kinase domain (KD) mutations decrease the sensitivity of the Abl kinase to imatinib, thus accounting for resistance to this inhibitor. Here we present the results obtained from a detailed molecular simulation study of the wild type and several mutant Abl KDs, amed at offering a comprehensive picture of the molecular mechanism of failure of the tyrosine kinase inhibitor binding to the mutated protein. **Materials and methods:** We calculated the binding free energy between imatinib and each protein as the sum of the molecular mechanical (MM) energies of the solute, the solvation free energies, and the solute entropic contribution. The version of MM/PBSA method used in this work took snapshots from a molecular dynamics (MD) trajectory of each drug/protein complex, with explicit water molecules and counterions. **Results:** Coupling the observations from the MD trajectories to the relevant energetic data (see Table 1) led to the conclusion that all analyzed mutations can be classified into two major groups: group A: mutations that play a major role in imatinib binding, and group B: mutations that play a modest role in imatinib binding. Mutations belonging to group A greatly decreases sensitivity of Abl toward Imatinib, and can be claimed to be the cause of resistance when identified in patients. Mutations found in group B can be further subdivided into two categories. The former includes those mutations for which the relevance in causing the resistant phenotype is questionable, and for which a dose escalation of the inhibitor would be expected to recapture a response. The latter

category groups all those mutations which will indeed be unresponsive to dose escalation, as no significant interaction is involved with the inhibitor. For these substitutions, we propose that they confer drug resistance through alternative mechanisms as, for instance, by interfering in the intramolecular regulation of c-Abl by the SRC Homology Domains 3 (SH3) and 2 (SH2) via a structural alteration of the contact point environment.

LB-63 A first-draft model of the BRCA1/BRCA2 network. Miguel Angel Pujana, Lea Starita, Jing-Dong Han, Muneesh Tewari, Jin Sook Ahn, Wael Elshamy, Volker Assmann, Rebecca Gelman, Kris Gunsalus, Jean-François Rual, Nicolas Bertin, Roger Greenberg, Bjian Bohian, Conxi Lazaro, David Hill, Katherine Nathanson, Barbara Weber, Jeffrey Parvin, Marc Vidal. Dana-Farber Cancer Institute, Boston, MA, Brigham and Women's Hospital, Boston, MA, University Hospital Hamburg-Eppendorf, Hamburg, Germany, New York University, New York, NY, Medical and Molecular Genetics Centre - IRO, Barcelona, Spain, University of Pennsylvania Medical Center, Abramson Family Cancer Institute, Philadelphia, PA.

To address the study of how cellular networks are affected or contribute to cellular transformation, we developed a strategy based on the generation of "first-draft" models of the networks built around known cancer gene products. Because its polygenic basis with undiscovered susceptibility and oncogenic genes, we chose breast cancer development as a test for the strategy. Through combinatorial analysis of functional genomic information as gene expression profiles, disease-associated genetic networks and systems-levels integrated networks we defined a "breast cancer gene module" with predicted novel functional relationships to known breast cancer tumor suppressors. Genes within this module encoded for novel functional relationships with BRCA1 and BRCA2, and novel protein circuits including these tumor suppressors were defined. Among the novel components identified we have functionally characterized the Hyaluronan-Mediated Motility Receptor (HMMR, human Rhamm). Our results suggest a critical role for HMMR in breast cancer development and that similar strategies could help to complete other cancer-related cellular networks and, thus, to understand how they are affected and/or contribute to cellular transformation.

LB-64 Integrated analysis of gene copy numbers and gene expression identifies clusters of genetically co-regulated genes and TOPORS as putative tumor suppressor gene in the human glioma genome. Markus Bredel, Dejan Juric, Claudia Bredel, Griffith R. Harsh, Hannes Vogel, Lawrence D. Recht, Branimir I. Sikic. Stanford University, Stanford, CA.

The integration of genetic data with gene expression data provides an effective approach for cancer gene discovery. It particularly enables the prioritization of seemingly random gene copy number alterations in tumors by assessing their effect on the transcriptomic level. This feature provides a first-pass means of distinguishing biologically irrelevant bystander genes from potential cancer gene targets. Utilizing advanced bioinformatics tools, we are presenting an analysis algorithm that combines circular binary segmentation (CBS) for the identification of gene copy alterations and gene copy number and gene expression data integration with a modification of signal-to-noise (s2n) ratio and s2n ratio moving average computation, and random permutation testing. This algorithm was applied to matched gene expression and array-CGH experiments in a set of 45 gliomas, utilizing 43,000-element cDNA microarrays. CBS analysis initially translated the raw intensity measurements into regions of equal gene copy number that were deemed changed if they fell into the 2.5%- or 97.5%-quantiles of distribution of all segmented values. s2n ratio computation and random permutation testing were then used to assess the influence of copy number aberration for each gene on its transcript and to assign significances to all computed ratios, respectively. 1,933 clones passed a probability threshold of 0.05. Since recurrence frequencies of genetic alterations in human tumors provide a