Thursday 9 November 08:00–09:45

PLENARY SESSION 4

Genomics and proteomics analysis

227 INVITED

From genes to drugs

S. Friend. *USA*

Abstract not received.

228 INVITED

Unbiased approach to identify predictive genetic markers for effects of cytotoxic agents

M.E. Dolan[1], S.J. Shukla[2], S. Duan[3], W.K. Bleibel[3], S.R. Huang[3], J.A. Badner[4], T. Clark[5], T.X. Chen[5], A.C. Schweitzer[5], J.E. Blume[6]. *[1]University of Chicago, Medicine, Chicago, USA; [2]University of Chicago, Human Genetics, Chicago, USA; [3]University of Chicago, Medicine, Chicago, USA; [4]University of Chicago, Psychiatry, Chicago, USA; [5]Affymetrix Inc, Santa Clara, USA; [6]Affymetrix Inc, Santa Clara, USA*

Little is known about heritable factors that influence chemotherapeutic-associated toxicity. Our goal is to better understand the genetic basis of drug toxicity. We employed a novel genome-wide approach to identify germline genetic variation responsible for hemotherapeutic cytotoxicity. Our approach combines linkage analysis, association and expression analysis. Cell growth inhibition of lymphoblastoid cell lines (LCLs) derived from members of large, healthy CEPH pedigrees and HapMap Yoruban trios was quantified following treatment with cisplatin, carboplatin, daunorubicin and etoposide for 48 or 72 hours. Population differences in cytotoxicity for carboplatin and daunorubicin were observed in cell lines derived from individuals of European and African descent. Significant heritability was indicated for IC50 of cisplatin ($h2 = 0.34$, $p < 1 \times 10^{-7}$), carboplatin ($h2 = 0.21$, $p < 3 \times 10^{-5}$) daunorubicin ($h2 = 0.29$, $p < 8 \times 10^{-6}$) and etoposide ($h2 = 0.25$, $p < 5 \times 10^{-5}$). Linkage analysis revealed 2 signals with LOD scores above 3 on chromosomes 2 and 11 for carboplatin. One region with a LOD above 3 was found for daunorubicin on chromosome 4. Overlapping linkage regions with suggestive LOD scores for 2 or more drugs were found on chromosomes 4, 11, and 16. Genes found under suggestive linkage peaks and that had significant SNPs associated with drug-induced cytotoxicity using HapMap samples were further evaluated using the Affymetrix Human Exon 1.0 ST Array. Our approach could lead to the discovery of genes that were previously unknown or unrecognized as important determinants of cytotoxicity. Shared genes for response to various classes of chemotherapeutic agents can also be evaluated. This approach can be applied to other phenotypes and drugs.
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229 INVITED

The role of genomics and proteomics in targeted drug development: discovery and use of biomarkers

P. Workman. *The Institute of Cancer Research, UK centre for Cancer Therapeutics, Sutton, United Kingdom*

Molecular diagnostics are required to identify patients most likely to benefit from molecular therapeutics. Molecular biomarkers are also needed for proof of concept of target inhibition and optimising dosing schedules. Drugging the cancer genome is possible as exemplified by trastuzumab, imatinib and others. But there is a long way to go. Many cancer targets and pathways remain undrugged. Only 5% of oncology drugs entering Phase I actually reach marketing approval. Many fail at a late stage. Identifying failing drugs early is essential so save huge costs. Success rates can be improved by focusing on those issues causing failure in the clinic. Previously, poor pharmacokinetics/bioavailability was a major problem. This was addressed by using high-throughput predictive assays to improve pharmacokinetic properties. Major causes of attrition in the clinic are now efficacy (30%) and toxicity (30%). Development of novel agents acting on new molecular targets is especially risky. Risk can be reduced by: (1) enhancing the quality of innovative drugs by prioritising the best targets, improving predictive animal models and fine-tuning physicochemical, biological and pharmacologic properties of clinical candidates; (2) using biomarkers to make clinical trials more intelligent and informative and decision-making more rational and effective. We developed the concept of the 'pharmacologic audit trail' (Workman Current Pharmaceutical Design 9 981 2003) that provides a logical and practical framework for tracking the performance of a drug during both preclinical and clinical development. It also provides a rational basis for assessing the risk of failure and for making informed decisions. The pharmacologic audit trail works by asking a series of hierarchically or sequentially arranged questions: What is the status of the molecular target? Are active concentrations of drug achieved in plasma and tumour tissue? Is the intended molecular target inhibited? Is the biochemical pathway modulated? Is the desired bjological effect obtained, eg cell cycle arrest, apoptosis? Is clinical benefit gained? As a drug progresses through the hierarchy of questions the risk of failure is reduced. It is essential to have robust, validated assays available for molecular biomarkers and pharmacokinetic behaviour. Advances in genomic technologies have enhanced biomarker discovery. Development of minimally invasive methods based on PET and MRS/MRI is particularly important.

230 INVITED

From biomarkers to clinical utility

M.J. Ratain. *University of Chicago, Department of Medicine, Chicago, USA*

The promise of predictive genomic and proteomic biomarkers to improve outcomes in oncology is unlimited. However, realization of this vision requires a careful stepwise approach, employing established principles of diagnostic development. These steps include: development of a reproducible and robust assay suitable for clinical samples collected from multiple research centers, retrospective studies, prospective studies, and confirmatory studies. Thorough consideration must also be given to measurement of the outcome of interest (i.e., clinical phenotype), which is often neglected in biomarker studies. In addition, it is usually critical to conduct at least one prospective study to avoid the biases and uncertainties of retrospective studies. This is particularly imperative for biomarkers that are not explainable by a body of preclinical data, such as in vitro association studies (e.g., in hepatic microsomes), functional genomics or pathway biology. Measurement of clinical utility is a particular challenge. It is not feasible to conduct prospective randomized studies of all diagnostic tests that have been demonstrated to predict for clinical outcomes. Although this may be appropriate in select circumstances, decision analysis tools may be sufficient, if the sensitivity, specificity, and positive/negative predictive value of the biomarker are well characterized. Specific examples of successful predictive biomarker development will be discussed, including examples from outside oncology.

Thursday 9 November 10:15–12:00

PLENARY SESSION 5

DNA checkpoints and the p53 pathway

231 INVITED

Activation of p53 by small molecules from fish to man

D. Lane, S. Lain. *Ninewells Hospital & Medical School, Department of Surgery and Molecular Oncology, Dundee, United Kingdom*

More than half of human tumours retain wild type p53 as determined by DNA sequence analysis. In these tumours pharmaceutical modulation of the p53 response by non-genotoxic small molecules may be valuable therapeutically. Recent work with small molecule inhibitors of the p53 Mdm2 interaction supports such a view. We have screened large numbers of compounds in cell based high throughput assays for activation of p53 transcription. A variety of secondary assays have been developed to determine the mechanism of action of these compounds. A number of potent "hit" molecules have been identified and one series with a novel mechanism of action has shown activity in xenograft models. One set of compounds acts by blocking nuclear export while another group acts by inhibiting RNA polymerase 11 phosphorylation. The use of selected drug combinations shows remarkable levels of synergy in p53 activation suggesting novel routes to treatment optimization. Recently we have developed a panel of monoclonal antibodies to Zebra fish p53. These antibodies work exceptionally well in immuno-histology allowing the ready evaluation of a drugs ability to stabilize p53 and providing a simple high throughput assay to study drug uptake and distribution.