Tuesday 28 September 13:15–14:00

Michel Clavel Lecture

1 INVITED

How to develop a successful cancer drug – molecules to medicines or targets to treatments?

H. Newell. *University of Newcastle, Cancer Research Unit Framlington Place, Newcastle upon Tyne, UK*

Cancer chemotherapy with either small molecules or blocking antibodies remains the only treatment modality with curative activity against multiple forms of metastatic malignancy. Over the past decade, cytotoxic and anti-endocrine therapies have been supplemented by targeted therapies that seek to exploit the molecular lesions that underlie the carcinogenic process or maintain the cancer phenotype. Success with, for example, imatinib and trastuzumab has suggested that identification and validation of the drug target is the starting point for the optimal route to the development of active drugs. However, in reality, our understanding of the biology of cancer is still too rudimentary to allow drug developers to rely on the simplistic linear pathway of target identification and validation, lead identification and optimisation, followed by Phase **I**, **II** and **III** trials. As pre-clinical and clinical drug developers prepare for the second wave of targeted agents it is worthwhile reflecting on experience gained during the initial development of cytotoxic drugs. For example, the clinical activity of alkylating agents and antimetabolites was demonstrated before the targets for these drugs were defined in any detail. Recent experience with signal transduction modifiers has again shown that agents initially developed to exploit one target may actually hit other targets, and that these other targets may be more important to the clinical activity of the compound. Indeed, the ability of individual compounds to interact with multiple targets may be a key factor that differentiates between active and inactive therapeutics. Thus, as with conventional cytotoxic agents, drug developers should design pre-clinical studies and early clinical trials in a manner that allows the effects of the drug to inform the development process.

Tuesday 28 September 14:00–14:45

Keynote Lecture

2 INVITED

Pitfalls in developing cancer chemoprevention agents

A. Decensi. *Italy*

Abstract not received.

Tuesday 28 September 15:15–17:20

PLENARY SESSION 1

Applications of proteomics and genomics in drug discovery

3 INVITED

Overview of proteomics with emphasis on diagnosis and monitoring

E.C. Kohn, E.M. Posadas, V. Espina, V. Kwitkowski, B. Davidson, E.F. Petricoin, L. Liotta. *NCI/FDA Clinical Proteomic Program, Medical Oncology Clinical Research, Laboratory of Pathology, Bethesda, USA*

Qualitative and quantitative assessment of the serum and tissue proteome is providing critical information to advance our understanding of cancer, its microenvironment, successes (or disappointments) in molecular therapeutics, and the future of cancer care. The number of advanced proteomic platforms and bioinformatics approaches have rapidly increased, as have their applications, such that we are now at the crossroads where identification of preferred platforms and focus of clinical questions is needed to recognize the promise of proteomics and to guide future developments. While in part controversial, it is clear that viewing tissue and serum proteomes using mass spectrometry has provided access to a previously uncharted low molecular weight proteome. The advent of sequence information from this archive and development of an protein database bank through the open exchange of raw data will allow the scientific community to benefit from these costly studies. Their use for biomarker development has been shown by numerous investigators to have promise in a variety of cancers including ovarian, prostate, breast, pancreas, and lung cancers. Pilot and validation clinical trials have been initiated in several cancers to further test this concept. Signal pathway profiling is a critical need in cancer for diagnostics and individualization of therapy given the explosion of small molecule molecular therapeutics, and for proof of concept of these agents in the target population. We have seen remarkable activity of most of the small targeted molecules in preclinical animal models and have been dashed with less than expected results by too many in the patient. Sometimes, experimentation has identified reasons for failure or success. This is demonstrated by the identification of the EGFR mutations in the small subset of lung cancer patients with remarkable responses to gefintinib, and demonstration of ATP-binding site mutations in imatinib-resistant CML. New proteomic techniques have been developed and validated from which to test proof of concept in patient material through the use of minimally invasive percutaneous biopsy, microdissection, and protein array technology. Exploration of the biochemical events in the patient in the context of molecular targeted therapy and combinations of therapies will focus the cancer community to its next step.

4 INVITED

High throughput genome sequencing for cancer gene discovery: BRAF and beyond

R. Wooster, P.J. Stephens, H.R. Davies, C. Hunter, G.R. Bignell, R. Smith, M.R. Stratton, P.E. Futrea. *The Wellcome Trust Sanger Institute, Cancer Genome project, Cambridge, UK*

Protein kinases are comparatively frequent targets for mutation in cancer and attractive for therapeutic intervention. To identify mutations in human cancer we have resequenced the entire protein kinase family in a series of breast cancer samples comprising of 18 primary carcinomas and 9 cell lines derived from primary tumours (all with a matched constitutional DNA sample). The annotated human genome contains 518 kinase genes. In total 35 megabases of DNA sequence was screened (1.3Mb/sample) from this set of breast cancers making this the most in-depth sequence analysis of human cancer to date. We identified seventy-seven somatic (tumour specific) mutations that altered either protein coding sequence or consensus splice-junction sequences. Additionally, we discovered 14 silent somatic mutations along with 1892 germline polymorphisms. No frequently somatic point-mutated protein kinase was identified in the samples sequenced. The breast cancers in this study had a diverse mutation spectrum and produced substantial evidence for a specific, but as yet un-attributed, mutator phenotype.

5 INVITED

Towards a high throughput platform for quantitative serum protein profiling

R. Aebersold, X. Li, E. Yi, P. Mallick, H. Zhang. *Institute for Systems Biology, Proteomics, Seattle, USA*

The availability of the complete human genomic sequence has catalyzed the development of new technologies for the systematic and quantitative measurement of genomic and proteomic profiles to define comprehensive molecular signatures of tissues, cells and body fluids in health and disease. Such signatures are expected to impact a wide range of biological and clinical research questions, such as the systematic study of biological processes and the discovery of molecular clinical markers for detection, diagnosis and assessment of treatment outcome. The generation of such signatures via proteomics technology requires that many (ideally all) proteins in a sample can be identified and accurately quantified.
The analysis of the proteomes of body fluids such as serum, plasma, CSF, urine, etc., are complicated by the fact that many proteins are modified, frequently by glycosylation, and that a few highly expressed proteins dominate the proteome. We have recently developed a method that eliminates the challenges imposed by protein glycosylation and at the same time, reduces the complexity of the samples being analyzed. The method is based on the selective isolation, by solid-phase chemistry, of those peptides that are *N*-glycosylated in the native proteins. These peptides are then analyzed by quantitative mass spectrometry and the such generated patterns analyzed by a suite of software tools developed for the purpose. We will demonstrate that such patterns can differentiate sera from healthy mice and mice with a chemically induced tumor and that peptides that distinguish sera of human individuals can be detected and identified.