Mutation and functional screening of candidate 'tumour driving' kinase genes will be perfomed subsequently in large series of tumour samples. High-throughput 454 direct sequencing is ongoing for a series of 13 kinases. Tissue arrays of >600 tumor samples are available to analyse protein expression and phosphorylation status of kinases.
In vitro activity of novel kinase inhibitors being developed for adult oncology against the peadiatric tumour-driving kinases will be tested, including readouts of target inhibition and pathway modulation. When no inhibitor is available, a novel generation of antisense oligonucleotide inhibitor drugs (LNAs) will be developed.
In vivo validation of efficacy for successful compounds will be performed in established xenograft models of the six childhood tumour types. KidsCancer Kinome will contribute to a better understanding of the unique paediatric tumour biology and to the development of new drugs.

14 INVITED

Early phase drug development in the Children's Oncology Group

P.C. Adamson[1]. [1]*The Childrens Hospital of Philadelphia, Division of Clinical Pharmacology and Therapeutics, Philadelphia, USA*

The major challenges in childhood cancer drug development include (i) target identification, (ii) development of agents for targets unique to pediatric tumors, (iii) prioritization of new agents for clinical development, (iv) determination of a recommended dose for non-cytotoxic drugs, and (v) the study of targeted agents in phase 2 combination trials. Prioritization of drugs to study in phase 1 routinely incorporates data emerging from the Pediatric Preclinical Testing Program (PPTP). To then improve the efficiency of phase 1 evaluation, the Children's Oncology Group has adopted a number of complementary strategies. First, we better utilize early phase data from adult trials and, unless drug disposition in children suggests significantly different doses are required to achieve the drug exposures associated with biologic effects, limit the number of dose level explored to four. Second, we have adopted the Rolling Six trial phase 1 design that will decrease the number of times trial enrollment is suspended, further shortening the overall timeline. Lastly, for drugs that primarily target leukemias, when scientifically rational, we first perform dose finding in children with solid tumors, or otherwise assure the adult recommended dose has acceptable toxicity, produces exposures in children associated with efficacy, and avoid dose escalation because of the high rate of inevaluability in this population. This approach is being utilized in a spectrum of phase 1 trials, including the study of EGFR, VEGF, src kinase, raf kinase, bcr-abl, IGFR-1, mTOR, aurora kinase A, alk and c-MET inhibitors. Evaluation of a spectrum of biomarkers, ranging from drug exposure (pharmacokinetic) studies to imaging modalities including PET scans, is routinely incorporated into early phase trials. When feasible, phase 2 randomized trials are being utilized for efficacy determination and further prioritization.

15 INVITED

Early drug development in the childrens' clinics in Europe

G. Vassal. *France*

No abstract received

Wednesday, 22 October 2008 08:00–09:45

WORKSHOP 3

Pharmacogenomics − where are we now?

16 INVITED

Pharmacogenomics of anticancer drug disposition: we aren't there yet

A. Sparreboom[1]. [1]*St Jude Children's Research Hospital, Pharmaceutical Sciences, Memphis, USA*

There is often a marked variability in drug handling between individual patients, which contributes to variability in the pharmacodynamic effects of a given dose of a drug. A combination of physiological variables, inherited characteristics and environmental factors are known to alter the relationship between the absolute dose and the concentration-time profile in plasma. A variety of strategies is now being evaluated in patients to improve the therapeutic index of anticancer drugs, by implementation of pharmacogenetic imprinting though genotyping or phenotyping of individual patients. Several strategies have been explored extensively in recent years to specifically evaluate the contribution of germline variants in genes with a confirmed or suspected role in the pharmacokinetics of oncology drugs. Identification of genetic factors associated with interindividual variability in the absorption and disposition of such drugs is potentially vital to predicting or eventually adapting appropriate, individualized doses. However, traditionally, pharmacogenetic studies in oncology have been mostly retrospective, uncontrolled, contradictory, and underpowered due to the limited number of patients evaluated that carry the variant genotypes of interest. In addition, genotype-phenotype association studies in oncology have typically focused on single candidate genes, or even single variants without consideration of the multiple-gene contributions and complexity of absorption and disposition characteristics of many agents. Furthermore, the possible clinical impact of inherited genetic variation may be dependent on drug dose, schedule, and concurrent or concomitant combination therapy, as well as on race/ethnicity of a particular target population. This suggests that large-scale population studies involving targeted pathway genotype or even genome-wide association approaches need be explored to further assess the multivariate contribution of variation in all these genes to explaining interindividual pharmacokinetic and -dynamic variability associated with anticancer drug treatment.

17 INVITED

Bioinformatics – from the bench to the bedside and back

G. Rajagopal. *The Cancer Institute of New Jersey, New Brunswick, NJ, USA*

Advances in biomedicine and its effective translation from the bench to the bedside (and back) requires the efficient and secure development and deployment of cyber-infrastructure (i.e. computing, network and storage platforms) in conjunction with analytic, and interpretive methods to optimize the integration and transformation of increasingly voluminous biomedical data from high-throughput experiments and Internet enabled medical devices. This includes research on the development of novel techniques for the integration of biological and clinical data and the evolution of clinical informatics methodology to encompass biological observations. The end product is newly found knowledge from these integrative efforts that can be disseminated to a variety of stakeholders, including biomedical scientists, clinicians, and patients that is targeted towards the goal of of realizing proactive, predictive, preventive, personalized and participatory health. In this talk, I will overview projects I have been involved in at the Cancer Institute of New Jersey where the above issues have been addressed with some success. I will outline our plans to take it to the next level by working in partnership with academia and Industry in New Jersey to address data integration/mining challenges that form a barrier to linking bench and bedside.

18 INVITED

Pharmacogenomics in colon cancer: Fantasy or Reality

H. Lenz[1]. [1]*University of Southern California, Norris Comprehenisve Cancer Center, Keck School of Medicine Division of Medical Oncology, Los Angeles, CA, USA*

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in both men and women in the United States with a predicted 149,000 new cases this year. Since the 1960s, 5-fluorouracil has remained the mainstay of therapeutic options in the treatment of advanced CRC with response rates of 20−25%. The introduction of newer agents such as oxaliplatin and irinotecan in combination with 5-FU have increased response rates to 40−50% in advanced disease and improved survival. The development of monoclonal antibodies targeting the epidermal growth factor receptor (EGFR) or vascular endothelial growth factor (VEGF) has demonstrated additional clinical benefit for patients with metastatic disease. However, many patients succumb to their disease and a significant proportion will experience severe chemotherapy-associated toxicities while deriving little or no benefit. In order to improve the treatment of CRC, efforts must be directed toward the identification of patients who are likely to respond to a specific therapy, those who will experience severe toxicities and those who will benefit from chemotherapy in the adjuvant setting. However, the utility of individual markers of response, toxicity and disease recurrence remains in question and efforts are now underway to develop multimarker profiles which can more accurately predict disease response. The science of pharmacogenomics is emerging as an increasingly useful molecular tool to investigate the disparity in drug efficacy by analysis of variations such as genetic polymorphisms in drug targets, metabolizing enzymes, transporters and influential receptors. Consequently, the identification of accurate and validated predictive and prognostic markers combined with an increasing arsenal of therapeutic agents will provide the clinician with the knowledge