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

and the means of tailoring a targeted and effective therapy to the select patients who benefit most from chemotherapy.
The use of pharmacogenetic profiling in CRC to predict clinical response and identify those patients susceptible to increased toxicity is still a developing field. To make progress, there must be more complete evaluation of these markers before genetic information can become a routine part of clinical practice. Retrospective analyses have clearly demonstrated the proof of principle in this approach. However, the design of new prospective trials must encompass a more comprehensive and disciplined approach with defined protocols, primary end points and increased statistical power. Only when this approach is adopted will the ambiguity be replaced with more definitive answers in regards to the predictive and prognostic value of these markers and their clinical implementation. Follow-up studies are also required to identify the functional significance of the many mutations and polymorphic variants that exist in the patient population, such functional information will inevitably assist in unraveling the complex and multi-faceted mechanisms of drug metabolism and cytotoxicity. Markers of response to the novel therapeutic drugs including bevacizumab, cetuximab and panitumumab must also be identified and rigorously validated so that the use of these agents can be targeted to those who will derive greatest benefit.

Presence and Future:

1. To identify patients that could benefit the most from chemotherapies (chance of cure, response).
2. Molecular Markers should be in included in all clinical trials to establish predictive and prognostic markers, as well as surrogate markers and validate target inhibition.
3. The selection of new combinations should be based on molecular targets identified in tumor.
4. Pharmacogenomis should be early in drug development to understand drug metabolisms and avoid life threatening toxicities.

Challenges:

1. The validation of the association of molecular markers with clinical outcome in prospective trials. It is encouraging to note that these efforts are already underway.
2. The refining of technologies and statistical methods in order to accommodate the complexity of the molecular map that may determine outcome.
3. The standardization of testing methods and results' interpretation.
4. The adaptation of these findings and methods to every day practice, especially in the community.

19 INVITED

High throughput genotyping and its possible applications in pharmacoepidemiology

D.G. Cox[1]. [1]*CNRS, UMR 5201, Lyon, France*

Over the last decade, the capacity to quickly, accurately, and cost-effectively genotype single nucleotide polymorphisms (SNPs) in large scale studies (thousands to tens of thousands of individuals) on high throughput platforms (hundreds of thousands to millions of SNPs) has exploded. The trigger for this explosion was the sequencing of the human genome in the late 1990s, followed by the description of "block" structure of the genome and the human HapMap. These milestones allowed us to estimate the number of "common" polymorphisms (minor allele frequency $\gtrsim$5%), and how many of these polymorphisms need to be genotyped to capture the majority (>80%) of the SNP variation in the genome.
Today, it is possible to genotype over one million polymorphisms in tens of thousands of subjects, known as "genome wide association studies" (GWAS). Much as the technology leading to GWAS has exploded, the number of GWAS publications has also exploded. However, the vast majority of these studies have focused on either dichotomous disease outcomes or anthropomorphic and/or clinically important measures. Additionally, the results presented to date have been limited to associations between single SNPs and the outcome of interest, ignoring the possible interaction between multiple SNPs and environmental factors.
In this presentation, I will provide a brief history of genome scans, followed by a description of the two major GWAS platforms (Affymetrix and Illumina) and their respective strengths and limitations. We will then discuss the main points to consider when planning and designing a genome wide scan. This will include discussion on sample selection and handling, budgetary considerations, statistical power and replication, and analysis plans. Finally, we will be able to expand our discussion into possible applications of genome scans in pharmacoepidemiology.

Wednesday, 22 October 2008 10:15–12:00

WORKSHOP 4

Phase 0 trials – are they necessary?

20 INVITED

Phase 0 microdosing studies as part of the learn/confirm approach to drug development

C. Garner[1]. [1]*Xceleron Ltd, Oncology, Heslington York, United Kingdom*

Failure to predict human drug metabolism and pharmacokinetics (PK) from laboratory animal, in silico and in vitro models may mean that promising new candidate drugs are dropped sometimes quite late in the development path. Over the past 10 years a new approach to gaining human drug metabolism information has been developed known as human Phase 0 or microdose studies. In these studies, a small sub-pharmacological dose of drug is administered to humans to obtain basic ADME/PK data. The approach is reliant on having available very sensitive analytical methods such as accelerator mass spectrometry (AMS) so that trace plasma concentrations of drug and metabolites can be measured. Typically Phase 0 studies can be conducted rapidly and cheaply such that it is possible to progress from bench to bedside within a six months timeframe. Phase 0 studies are most effective when used to examine the PK of a number of drug candidates in order that a lead molecule can be selected to take on to a full Phase I study. In addition to human PK information, Phase 0 studies can establish if the drug reaches the relevant target tissue through removal of a small surgical or biopsy sample followed by drug and metabolite analysis by AMS. Concerns have been expressed that Phase 0 PK data will not be dose proportional to that seen at therapeutic doses. We have been examining this relationship over the past few years and have found an approximate 80% correlation between the dose levels. Some of this data will be presented together with examples of how Phase 0 PK data impacted on drug development.

References

Garner R C and Lappin G (2006) Commentary. The Phase 0 microdosing concept. Br J Clin Pharm, 61, 367–370.

21 INVITED

Use of phase 0-changes in cancer drug development

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Change is a continuous element in the design for first-in-human studies. Some changes are mostly incremental; others are major shifts in goals and approaches. The most important change over the last decade has been the type of compound entering the clinic. The contemporary emphasis upon molecularly-targeted agents has accelerated the trend towards correlative studies, but the results of these investigations remain as secondary findings behind the classic endpoints of toxicity and occasional tumor shrinkage. The term "Phase Zero" is intended to signify a major change in the structure of first-in-human studies of anticancer drugs. It is not simply an extension of the trend towards more biomarker studies. The enormous difference for Phase Zero is that pharmacodynamic or biomarker studies are not simply correlative. Evaluation of target modulation is now the primary goal, and is intended to inform decision-making regarding further compound development. There is always some blurring of the end of discovery and the beginning of development. For many investigators, the first-in-human experience is viewed as the end of discovery and the beginning of development. Phase Zero studies are explicitly designed to extend the process of discovery into first-in-human studies, obtaining information that will shape the beginning of the development process that will follow next.
The key to decision-making is the identification of the pivotal information for a "stop-or-go" decision. The design of the first clinical study must be customized to obtain that information. Because each compound and target is different, the most important information for each trial will vary. For some cases, choosing among analogs might be the goal, and the key information might be pharmacokinetic, such as extent of absorption or half-life in the body. For most target-oriented programs, pharmacodynamic measures are most important. If the compound is intended to inhibit an enzyme in the tumor, determination of inhibition is the primary objective. For receptor blockage strategies, the occupancy of the receptor by the compound is the desired information. For imaging studies, receptor and/or compound biodistribution is likely to be the most useful information.