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

WORKSHOP 1

Animal models in drug development

7 INVITED

Developing combination therapies for hormone-refractory prostate cancer in a pre-clinical mouse model of the disease

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Although most men diagnosed with early stage prostate cancer have favorable outcomes, those with advanced disease and particularly hormone-refractory prostate cancer eventually succumb to lethality since treatment options are limited. We have been investigating targeted therapies for the treatment of advanced prostate cancer using a relevant genetically-engineered mouse model of the disease, namely the *Nkx3.1; Pten* mutant mice. Based on previous studies showing that the Akt/mTOR and Erk Map kinase signaling pathways cooperate in prostate cancer progression, we have now performed pre-clinical studies in the *Nkx3.1; Pten* mutant mice to examine the consequences of combinatorial inhibition of these signaling pathways for prostate tumorigenesis in androgen-dependent and -independent contexts. We report that combination therapy using Rapamycin, an inhibitor of mTOR, and PD0325901, a MEK inhibitor, is potently anti-tumorigenic in the *Nkx3.1; Pten* mutant mice, particularly in contexts of limiting androgens. Furthermore, we find that these signaling pathways are coordinately de-regulated during prostate cancer progression in humans. Based on these pre-clinical studies in the mutant mice and the supporting data from human prostate cancer, we propose that combination therapy targeting the Akt/mTOR kinase and Erk Map kinase signaling pathways may be effective for treatment of patients with advanced prostate cancer, particularly in conjunction with androgen deprivation therapy.

8 INVITED

Pitfalls for cancer drug discovery with "genetic" animal models

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Background: The availability of animal models, primarily mice, engineered to possess single or multiple genetic abnormalities present in tumors raises the possibility that such animals would be useful in the discovery of novel agents directed against corresponding tumors in humans.
Materials and Methods: Retrospective review of published literature.
Results: A number of factors can conspire to limit the utility of genetically engineered animal models for cancer drug discovery. These factors may arise at the level of the drug, the tumor, and the host. At early stages in a drug candidate's preclinical evaluation, the exact molecule that will ultimately enter the clinic is often not defined. Hence, relatively large numbers of uniformly staged animals must be available to assess a number of candidate compounds. The variable penetrance of the maligant phenotype, and its relatively unpredictable evolution would require an extended duration of administration, ideally by the oral route. The pharmaceutics of the candidate molecule, usually poorly defined, further complicate the delivery and dosing uncertainties. From the standpoint of the tumor, concern must be raised that the the genetic abnormalities present in the tumor realistically mirror a human disease, including not only with the presence or absence of a single gene, but ideally also reflecting the presence or absence of parallel or competing molecular pathways and with a tissue context present in the human disease. These variables are imperfectly understood at the present time for most human tumors. Also, as the relevant tumors are of murine origin, systematic differences in sensitivity to an agent by murine cells may falsely predict either presence or absence of activity or toxicity when the same genetic lesion is present in a human cellular context. From the standpoint of the host, systematic differences in absorption and elimination mechanisms, plasma protein binding, and tolerable pharmacology comparing mice to humans could limit the predictive value of genetically altered murine hosts, as is also true for mice bearing more usual xenografts. All of these features argue against the use of engineered animals early in a drug candidate's discovery cycle. In contrast, once a drug candidate has been selected by more conventional criteria, and ideally when the agent already has available early phase human clinical trial information, engineered animal models could be quite valuable in defining patient subsets that might derive value from an agent, as well as suggest pharmacodynamic and perhaps predictive markers that would be applicable to the later stage clinical development of the agent.
Conclusion: Genetically engineered animal models most likely will be of greater utility later, rather than earlier, in a drug's discovery and development cycle.

9 INVITED

How naturally occurring cancers in dogs can inform the drug development path

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Opportunity: This session will focus on the opportunity to include naturally occurring cancers that develop in pet dogs, as translational models, in the development path of new human cancer drugs. Naturally occurring cancers in pet dogs and humans share many features, including histological appearance, tumor genetics, molecular targets, biological behavior and response to both conventional and novel targeted cancer therapies. Indeed, the formal integration of studies that include pet dogs with cancer has now begun and is becoming a more common part of an innovative cancer drug development process.
Background: The long history of dogs in biomedical research, their strong anatomic and physiologic similarities to humans, and the number of pet dogs that are diagnosed and managed with cancer each year (United States est. 1 million per year) supports the potential translational value of new cancer evaluation in large and outbred animals. Cancers developing in these animals are naturally occurring, with the tumor, the host and the tumor microenvironment all being syngeneic. Tumor initiation and progression are influenced by similar factors in both human and canine cancers, including age, nutrition, sex, reproductive status, and environmental exposures. The spectrum of cancers seen in pet dogs is as diverse as the cancers seen in human patients. Not surprisingly the genetic events that are understood to be associated with cancer development and progression in humans are the same as those that occur in canine cancers. The biological complexity of cancers in pet animals is high and emerges from a similar intra-tumoral (cell-to-cell) heterogeneity seen cancer in human cancer patients. A natural consequence of this heterogeneity is the acquisition of resistance to therapy, recurrence of disease, and metastasis to distant sites. Since there are no gold standard treatments for pet animals with cancer, new cancer treatments can be provided to pet dogs with cancer at earlier stages of progression than human trials. Flexibility in the conduct and design of trials that include dogs with cancer permits serial biopsy of tumor and collection of biological fluids, and imaging endpoints during exposure to novel cancer agents. Lastly, the rates of cancer progression are notably faster in pet dogs than humans, accordingly these studies can be completed without interruption to the existing development path. Implementation: In an effort to develop this novel cancer drug development opportunity, address potential risks with this approach and to establish the organizational infrastructure to undertake translational clinical trials in pet dogs, the United States National Cancer Institute's Center for Cancer Research has recently launched the Comparative Oncology Program. Through the NCI Comparative Oncology Program a multi-center consortium of veterinary colleges (COTC: Comparative Oncology Trials Consortium) have begun preclinical studies including pet dogs with cancer. These studies have been initiated and integrated within the preclinical and clinical development path for new cancer drugs. The COTC trials are based on collaboration and partnerships between academic institutions, the NCI and the pharmaceutical industry. We expect that studies that include pet dogs with cancer will inform and improve the development of new cancer drugs through answers to many questions not currently answered by conventional preclinical and early human clinical trials.

10 INVITED

Imaging signaling pathways in animal models

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The emerging fields of genomics and proteomics have led to a better comprehension of the pathophysiology of cancer and the identification of novel signaling pathways. These pathways offer novel targets which has led to the development of lead molecules designed to inhibit the signaling derived from these pathways. However, this poses a tremendous challenge for selecting and/or validating these targets and for broad profiling of lead molecules for candidate selection. Molecular imaging technologies have the potential to address these scientific and technological challenges. We have developed strategies wherein activation or inhibition of key pathways in tumor formation as well as in the response of tumors to therapies can be non-invasive imaged. Specific targets whose function can be quantitatively and dynamically monitored in living subjects include receptor tyrosine

kinases (EGFR, C-Met), serine/threonine kinases (Akt, GSK3-beta) as well as cytosolic (Caspases) and golgi resident proteases (furin). This work has resulted in the development of tools that have become invaluable in testing the efficacy of targeted therapeutic agents as well as in optimization of their dose, schedule and development of the most efficacious combination therapies.

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WORKSHOP 2

Paediatric Oncology

11 INVITED

Update on the application of the EU paediatric regulation

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Immediately effective in all EU member states, the Paediatric Regulation (EC) 1901/2006 came into force about 18 months ago (26/01/2007). Its high-level goals are to facilitate the development and availability of medicinal products where there is a paediatric need, to ensure that such products are subject to ethical research of high quality, and to improve the information available on such medicinal products. The European Medicines Agency with the network of National Agencies is responsible for the scientific evaluation, authorisation and surveillance of medicinal products in Europe, and recently the paediatric development according to the Paediatric Regulation.

For each product to be authorised for the first time or, e.g., for additional indications, a Paediatric Investigation Plan (PIP) or a waiver request, has to be submitted by the pharmaceutical company. Such plans should include measures for the development and for the generation of data that are sufficient for authorisation, including formulation aspects, non-clinical studies and clinical trials. The plans have to define the necessary data on quality, safety and efficacy for use in the paediatric population (0−18 years). Submission of a PIP has to be by end of phase 1 trials in adults for new products. Then, the plan is discussed, modified, and agreed or refused by the EMEA's scientific Paediatric Committee. The EMEA Decision on the Committee's opinion is binding on the company, and a summary is published. The development is most often a combination of requirements for studies, and of waivers; studies may be deferred until more data are obtained in adults. Waivers may be granted for subsets in whom the condition does not exist, or when studies are not justified by an expected therapeutic benefit).

From August 2007 to April 2008, in total 178 applications (corresponding to 326 indications) for PIPs or waivers were reviewed by the Committee. About 20% of the applications were for waivers. Each PIP application corresponds to one active substance (or a combination), but a PIP usually covers more than one indication (e.g., high-grade glioma and neuroblastoma). 14% of the applications were for the therapeutic area of oncology. After excluding applications for waivers only, oncology plans were proposed for 18 active substances, of which 6 were non-cytotoxic and/or targeted. Among applications for substances specifically targeting molecules or pathways, some were for first-in-class products, and some with a known mechanism of action. Therefore, potential scenarios for paediatric development and use have to be defined, including generating the data where there is an unmet medical need. The clinical trials proposed by companies for 15 active substances for paediatric oncology development included 4 phase 1/2 studies, 10 single-arm, most often single-agent phase 2 studies, and 4 phase 3 studies; in total, 8 combination-therapy studies were proposed.

The limited opportunities for clinical trials especially in paediatric oncology, the need to avoid repeated studies in case of similar mechanism of action and use, the vulnerability of the paediatric patients who lack legal competence to consent, all have implications for the design and the analysis of trials, which should only be performed by trained investigators. Ethics Committees also need appropriate paediatric expertise to balance the benefits and risks of research in children. As for paediatric development in general, the possibility for extrapolation of efficacy from adult studies has to be considered for paediatric oncology and haematology. The overall aim is, however, to address potential paediatric uses and not just very advanced cancer stages. Thorough non-clinical studies and paediatric models are increasingly proposed in PIPs, but need to be further developed in respect of non-cytotoxic and/or targeted active substances.

12 INVITED

The Pediatric Preclinical Testing Program (PPTP): changing the paradigm for drug development

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Background: Development of new therapies for children with cancer presents challenges unique to this population. The incidence of cancer is relatively low; in the United States about 12,400 new cases are diagnosed annually in patients under 20 years old, the overall cure rate is approaching seventy percent, and in many patients that ultimately fail curative therapy, initial responses to current multimodality treatments are good. Thus, there are relatively few patients eligible for experimental drug evaluation, and greater than 400 cancer therapeutics are under development. The primary objective of the PPTP is to identify novel agents that will have significant activity against childhood cancer.

Methods: We have established and molecularly characterized 60 in vivo xenograft models and 23 cell lines representing most of the common cancers in children including neuroblastoma, sarcomas (osteosarcoma, Ewing, rhabdomyosarcoma), brain tumors (ependymoma, medulloblastoma, glioblastoma), kidney tumors (Wilms, rhabdoid) and acute lymphoblastic leukemia (ALL). Seventy five percent of the models were derived directly from patient specimens engrafted into mice, and 25 derived at relapse. In vivo we have evaluated 'blinded' the activity of 25 agents including standard cytotoxic agents used in the treatment of childhood cancer, novel agents in early clinical development, and several combinations of novel and standard agents.

Results: Molecular characterization (Affymetrix U133+2, 100K SNP) showed the models selected for the PPTP panels accurately recapitulated the molecular profiles of patient samples. Standard cytotoxic agents (cyclophosphamide, vincristine) demonstrated high activity against appropriate models, thus validating the screen. The screen has identified an antibody against the IGF-1 receptor (SCH717454), an Aurora A kinase inhibitor (MLN8237) and a picornavirus (SVV-001) as having high activity in various histotype panels.

Conclusions: The tumor panels established in the PPTP accurately recapitulate the molecular characteristics of their respective histotypes, and identify known active chemotherapeutic agents. Prospectively, the screen has identified novel agents with high activity that are being 'fast tracked' for pediatric clinical trials. Clinical evaluation of agents both active and inactive in the PPTP screen will determine the validity of this approach to selecting agents that warrant prioritization for pediatric testing.

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13 INVITED

KidsCancerKinome: a EU-FP6 project for preclinical kinase inhibitor evaluation as a tool to prioritize compounds for paediatric development

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KidsCancer Kinome will make a comprehensive analysis of the human protein kinase family. Protein kinases are already excellent targets for many small inhibitory molecules and antibodies designed for adult tumours. Six aggressive childhood tumours (neuroblastoma, medulloblastoma, rhabdomyosarcoma, osteosarcoma, Ewing sarcoma and acute lymphocytic leukaemia) will be addressed. These six tumours are responsible for 50% of childhood cancer deaths.

RNAi knockdown of kinase expression by viral shRNA libraries will be applied to test the human kinase gene family for tumour-driving kinases in cell lines. We first focus on the 'drugged kinases'. Effective lentiviral shRNA vectors are currently being tested for CDK2, AURKA+B, IGF1R, ALK and PIK3CA kinases in cell line panels of each of the 6 tumours. The next series of kinases will include KIT, MET, AKT3, FYN, MEK5+6, PDGFRA, PLK1 and RAF1.