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