design of a phase I study and in the selection of the dosing strategy and treatment schedule. Optimal use of the preclinical PK−PD database may improve the selection of dose and schedule in early clinical studies and facilitate the execution of these studies, thereby reducing the length of the studies, number of patients needed and patients that are being exposed to sub-therapeutic doses. An example of the implementation of such strategy is the clinical development of the a2-integrin inhibitor E7820 whereby the expression of a2-integrin on platelets and tumor cells served as a biomarker. Another example is the PK−PD modeling of the multitargeted tyrosine kinase inhibitor E7080 (HOPE). By applying PK−PD and modeling the magnitude of the effect of antihypertensive therapy could be predicted on the dose-limiting hypertension and proteinuria upon treatment with E7080, demonstrating the usefulness of the outlined methodology.

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26 INVITED

Is a side effect of molecular targeted therapy a marker of efficacy?

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The target of signal transduction inhibitors may be present on normal as well as tumor cells, what explains the side effects in addition to antitumor activity of molecular targeted therapy. Some toxicities may be a pharmacodynamic effect of pathway inhibition (mechanism-based toxicities) and, in tumours that depend on the inhibited pathway for proliferation, a biomarker of efficacy. Hypertension, a recognized adverse event of angiogenesis inhibitors, may be a potential biomarker of VEGF pathway inhibition and, in some occasions, of efficacy. Retrospective analyses of various studies with bevacizumab, sorafenib, sunitinib, and axitinib have verified that early development of hypertension correlates with clinical outcome in patients with different tumour types, including advanced colorectal, breast and renal cell carcinoma. In addition, several studies have suggested that development of rash with treatment with tyrosine kinase inhibitors or monoclonal antibodies against EGFR is associated with improved outcomes in patients with non-small-cell lung cancer, head and neck, colorectal and pancreatic cancer. Response rates as well as progression-free and overall survivals have improved in patients that develop skin toxicity with anti-EGFR targeted agents, such as erlotinib, gefitinib, cetuximab and panitumumab. The development of hypertriglyceridemia with mTOR inhibitors and hyperglycemia with PI3K/AKT inhibitors are pharmacodynamic effects of pathway inhibition and the potential value as markers of efficacy is under evaluation. However, the predictive value of a side effect requires validation in prospective trials, like the "dosing-to-rash" studies that are currently underway. Oncogene addiction on a specific pathway that is targeted with the therapy may be the possible link between a mechanism-based adverse event and efficacy. In addition, biological basis for this association may be pharmacological, with subjects with higher plasma levels of the drug attaining greater toxicity and antitumor response, and also genetic, as single nucleotide polymorphisms play a role in drug pharmacokinetics and pharmacodynamic processes. Additional studies are of utmost importance for further clarifications of this correlation.

27 INVITED

Drug response in a genetically engineered mouse: clinical implications

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The progress in the development of new anticancer agent's remains rather slow. One of the bottlenecks in anticancer drug development is the lack of predictive preclinical models. Conventional cancer models, based on cultured cell lines and xenograft derived from these cell lines are poor predictors of clinical outcome. In addition, as these models do not represent well the full heterogeneity of the disease have not been very useful as platforms for biomarker discovery. Recently, there has been interest in the newer models for anticancer drug development including genetically engineered mouse models and as well as freshly generated xenograft obtained directly from cancer patients. These models have several biological features that suggest may be predictors of clinical outcome. These included a more diverse and close to human cancer spectrum of genomic alterations, and the presence of stroma and cancer stem cells. A series of recent studies demonstrate that these preclinical models are suitable for biomarkers discovery and, in fact, some of the biomarkers currently in clinical use could had been discovered in preclinical models. Emerging data also suggest that these models are better predictors of the outcome of clinical trials indicating that could be useful for drug screening and design of clinical trials. Indeed, it is expected that these models will be progressively used in drug development in lieu of extensive clinical programs as it will permit a much focused clinical plan. Finally, these models look promising as platform for personalized cancer treatment. However, additional data is needed to fully determine their role in this setting.

Current representative preclinical models. drugs in patients with pancreatic cancer. Multiple clinical trials conducted in this disease have been negative. While the ultimate progress in pancreatic cancer will come from the discovery of new drugs and strategies, it is also clear that a better understanding of drug mechanism of action and expected antitumor effect may help in clinical development. If could also be argue that some agents form which preclinical results are not optimal should perhaps not be developed clinically so that resources can be prioritized and focused in those compounds with a better chance. It is noteworthy that most new agents tested in the clinic are selected with very limited preclinical information. In general, studies are limited to a few conventional cell lines at the most. It is doubtful that these cell lines, which have adapted to growth in culture for prolonged periods of time maintain are predictive of pancreatic cancer clinical outcome.

More recently, two models of pancreas cancer have become available which may facilitate the clinical development of new agents. Using genetically engineering techniques several groups have developed genetically modified mouse models which faithfully recapitulate the development and clinical presentation of the disease in mice. While these models were initially used to understand the molecular biology of pancreatic cancer, more recent studies have used these models for drug testing. In parallel to this work, other groups including our own have developed personalized pancreatic cancer tumors using patient derived tumor materials obtained at the time of surgery and propagating these tumors in nude mice. We have used this platform to perform drug screening studies, biomarker development and to design personalize treatment strategies. This work has already identified interesting new targets and strategies which are been advanced to clinical development.

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27A

Targeting the PI3K/mTOR pathway in genetically engineered mouse models of advanced prostate cancer

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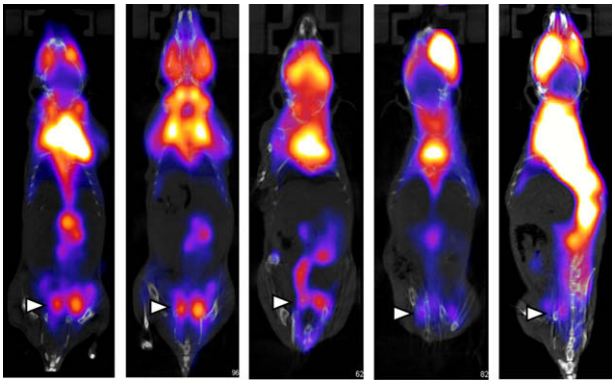
The PTEN and p53 tumor suppressors are among the most commonly inactivated or mutated genes in human cancer, including prostate cancer. Loss of PTEN is associated with increased pathologic Gleason score and risk of clinical recurrence, and 20–60% of human metastatic prostate cancers have loss of heterozygosity at the PTEN locus, resulting in hyperactivation of the PI3K/mTOR pathway. Mice with germline heterozygosity for PTEN have been shown to develop prostate intraepithelial neoplasia (PIN) at a high rate (>60%) and mice with prostate specific homozygous deletion of PTEN develop invasive prostate cancer, albeit with prolonged latency. Combined inactivation of PTEN and p53 in mouse prostate elicits invasive cancer by 9 weeks of age and invariable lethality by 7 months of age. We evaluated the impact of GSK48 (dual PI3K/mTOR inhibitor) in prostate-specific PTEN/p53 double knockout mice and prostate-specific PTEN mice, respectively. The mice were imaged by 18FDG-PET and T2-weighted MRI, respectively, for baseline tumor metabolic and volumetric assessment prior to drug administration. GSK458 was

administered at 3 mg/kg by daily oral gavage for 3 weeks with serial 18FDG-PET and T2-weighted MRI imaging at 2 days, 1 week, 2 weeks and 3 weeks post-treatment respectively, followed by sacrifice, prostate harvest and standard hisopathologic and immunohistochemical staining. GSK458 treatment of PTEN/p53 and PTEN mice results in adequate target inhibition, based on pharmacodynamic assessment by 18FDG-PET uptake. There was a significant reduction in tumor burden in both intraepithelial and poorly differentiated atypical components within stroma and partial stromal collapse following 3 weeks of GSK458 treatment, as assessed by MRI and histopathology. MRI assessment suggests that there may be partial regrowth of tumor at the end of 3 weeks of treatment with GSK458, suggesting acquired resistance. These data demonstrate that GSK458 treatment of prostate-specific PTEN/p53 double knockout and PTEN knockout mice, respectively, results in a pharmacodynamic and antitumor response with potential development of acquired resistance. The results underscore the utility of genetically engineered mouse models to predict response to targeted therapies in genetically stratified human clinical trials, and elucidate mechanisms of acquired resistance early in clinical development. The design of rational combinations to overcome resistance to PI3K-directed targeted therapies are also being explored in these genetically engineered mouse models systems.



Day 0	Day 1	Day 2	Day 8	Day 16
	20h after treatment	3h after treatment	22h after treatment	22h after treatment
100% (baseline)	121% (baseline)	34% (baseline)	57% (baseline)	59% (baseline)

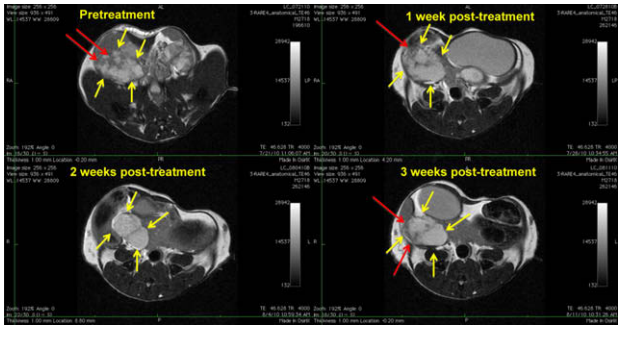


Figure: Impact of GSK458 (PI3K/mTOR inhibitor) on prostate tumor 18FDG-PET uptake and antitumor response in prostate-specific PTEN-p53 double knockout mice. The mice were treated with GSK458 (3 mg/kg) by continuous daily dosing for 3 weeks. Baseline pre-treatment (day 0) and indicated post-treatment (A) PET-CT and (B) MRI scans, respectively, were obtained to serially assess for target inhibition and antitumor response

Wednesday, 17 November 2010 10:15–12:00

WORKSHOP 6

New drug development in the 21st century: Do we need to break from tradition?

28 INVITED

The point of view of academia

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Owing to the explosive progress in biomedical and pharmaceutical research in the area of cancer biology and a better understanding of the different molecular pathways that drive tumorigenesis, the number of new molecular entities that enter into the development process has increased significantly. However, the rate of approval for marketing of anticancer agents is very low; estimated to be less than 10%.

One of the main limitations of the current drug development paradigm is the lack of a clear target population. This underlines the need to identify biomarkers that can define more precisely which patients will truly benefit from which drugs. Only few biomarkers have attained the level of validation needed for routine clinical use so far, probably due to the current very suboptimal process of biomarker discovery and validation.

Early clinical trials represent a crucial bridge between preclinical drug discovery and the resource-intense randomized phase III trial-the definitive regulatory hurdle for drug approval. High attrition rates and rising costs, when coupled with the extraordinary opportunities opened up by cancer genomics and the promise of personalized medicine call for new approaches in the conduct and design of clinical trials. The key challenges lie in increasing the odds for successful and efficient transition of a compound through the drug development pipeline, as well as in better identifying subsets of patients who truly benefit.

Our growing knowledge of the genetic landscape of cancer is providing the basis for a new generation of prognostic and predictive biomarkers. There is tremendous scope for these biomarkers to contribute to the drug development process, with the aim of increasing the success rate, accelerating the timeline of new molecularly targeted therapies to regulatory approval and patient benefit, and ultimately facilitating the implementation of personalized cancer medicine.

Coupling of smaller 'proof of principle' studies with larger registration trials offers the promise of speeding up the time to market of new therapies. Clever new designs can provide valuable insight regarding mechanisms of action of and resistance to novel drugs by identifying patients who are most likely to respond to a novel therapy early in the drug development process. Armed with new omics, prospective translational research, and international collaboration, we are well on our way to break from tradition and open a new chapter of drug development.

The NEOBIG initiative will be summarized as it represents one attempt at a more efficient and targeted drug development in breast cancer.

Finally, the importance of a healthy collaboration between academia and pharma will be emphasized: models for such a collaboration now exist and represent a "win-win" situation for both parties as well as the best way of keeping faith with trial participants.

29 INVITED

In search of intermediate endpoints

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The major goals of cancer drug development are to identify new agents that improve the *quantity* or *quality* of patient survival, with acceptable adverse effects. Furthermore, increasingly in today's environment of molecular targeted treatment, it is expected that, in the course of drug development, criteria for selection of patients most likely to experience benefits or least likely to experience serious adverse effects will be identified.

Endpoints of studies that definitively address these goals include *overall or relapse free survival* as well as *patient reported outcomes* using validated Quality of Life instruments. Studies evaluating these outcomes generally occur at the end of a long road of early phase trials, have large samples sizes and are randomized in design. Some of these randomized trials may also include integration of (putative) selection biomarkers with the aim of validation within the definitive randomized trial.

The cost in terms of time, patients, expectations and funding is high when agents fail in phase III or when there are lost opportunities to identify predictive biomarkers. Early rejection of agents *likely to be inactive* should increase efficiency but requires use of endpoints occurring earlier