[GI_{50} value = 130 nM] and SNU-16 [GI_{50} value = 690 nM]). Concentration-dependent inhibition of phosphorylation of downstream FGFR signals (FRS, MEK, ERK, and AKT) is evident in response to ARQ 087 treatment. In addition, growth of SNU-16 gastric carcinoma, AN3CA endometrial cancer, and FGFR2-transfected Ba/F3 tumor xenografts in athymic mice was markedly suppressed after daily oral administration. Finally, ARQ 087 shows favorable pharmaceutical properties that warrant its consideration as a candidate for future clinical development.

120 POSTER

Primary tumor derived preclinical model mimics human colon cancer: a novel platform to study cancer biology and to evaluate anti-cancer drugs

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Background: Colon cancer is a major cancer in developed and developing nations for which, the underlying mechanism of initiation, maintenance and progression is relatively unknown. The preclinical models used to understand the biology of colon cancer were, till recently, less valuable largely due to lack of consistency in maintaining intra-tumor heterogeneity and tumor microenvironment. At present, established cancer cell lines and cell line based allograft or genetically engineered mouse models are being used for testing personalized therapeutics. However, these models often fail to mimic the real disease and therefore have had limited success as predictive platforms. In order to understand the biology of cancer pathways and testing novel anti-cancer agents, we have developed a novel organotypic explant culture and xenograft models using primary tumors from treatment naïve patients.
Materials and Methods: In this organotypic culture we used paracrine growth factors or ligands for receptors that were derived from the same patient. Extensive profiling of these tumors was performed using transcriptomics and phospho proteomics to provide a mechanistic insight of this system. As proof of concept, advanced stage colorectal cancer explants were treated with oxaliplatin at different concentrations for 4 days. Further freshly isolated treatment naïve primary tumors from patients was propagated in immune compromised mice and treated with oxaliplatin. Anticancer effect of oxaliplatin was evaluated by immuno-histochemical and biochemical analysis.
Results: Data indicate that presence of autologous human ligands significantly enhance the survival and viability of tumor cells due to signal induced activation of key oncogenic pathways. Dose and time dependent effect of oxaliplatin was observed in these models. Molecular profiling and histological data from both primary and xenografted tumor maintained in mice are very similar which suggests that these models preserve the pathological characteristics of primary tumors.
Conclusion: Our data indicate that signaling pathways responsible for tumor growth require human ligands for the activation of downstream signaling network in ex vivo setting. Anti-tumor efficacy of oxaliplatin in explant and primary human derived xenograft models correlates with the clinical outcome which suggest that these models might be useful to predict the treatment options for patients.

121 POSTER

Functional role of CD133 in glioblastoma multiforme

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Background: Glioblastoma multiforme (GBM) is a cytologically malignant tumour of the central nervous system, associated with poor prognosis and fatal outcome (5 year survival, <6%). Such tumours are believed to be initiated and maintained by a subpopulation of cells, which resemble normal adult stem cells. Cancer stem cells (CSCs), may contribute to the chemo-/radio-resistance exhibited by these tumours and can be identified using the immunocytochemical marker CD133. This pentaspan membrane protein is associated with increased tumorigenicity, chemo-/radio-resistance and poor prognosis. In this study we investigated the functional role of CD133 in the progression of GBM to elucidate any therapeutic benefits of modulating CD133 expression.
Materials and Methods: CD133-specific siRNA and siPORT-Amine transfection reagent were used to achieve knockdown of CD133 in GBM cell lines. Gene and protein expression were measured over time using real-time PCR and FACS, respectively. GBM cell lines were cultured in 1% oxygen to induce hypoxia. Transient knockdown of hypoxia-inducible factors (HIF) was achieved using HIF-specific siRNA, in hypoxic conditions. Biological functions of CD133 were assessed by performing wound-healing assay to investigate migration; MTT to measure the rate of proliferation; neurosphere formation to assess tumorigenicity; and etoposide drug challenge to assess chemo-resistance.
Results: Hypoxia upregulated CD133 expression by 4-fold ($p < 0.001$; $n = 3$) compared to cells cultured in normoxia. Knockdown of hypoxia inducible factors resulted in the downregulation of CD133 in hypoxia. For example, in GBM cell line U251, HIF2-α knockdown resulted in a significant reduction in CD133 gene expression (60% downregulation; $p < 0.01$; $n = 5$). CD133-specific siRNA successfully knocked down gene expression of CD133 (85% knockdown; $p < 0.0001$; $n = 3$) leading to significantly reduced migration ($p < 0.001$; $n = 3$); increased susceptibility to chemotherapeutic agent etoposide ($p < 0.05$; $n = 3$); and reduced neurosphere forming potential ($p < 0.05$; $n = 3$) in GBM cell lines. No change in cell proliferation was noted.
Conclusions: Hypoxia, via HIF-2a, increases CD133 expression in GBM cells. CD133 expression alters important biological properties of GBM cells with CD133 knockdown reducing their migration ability, tumorigenicity and sensitivity to chemotherapeutics. Therefore, using CD133 targeted therapies, in combination with established standards-of-care may improve GBM patient outcome.

122 POSTER

Novel class I PI3K inhibitor CH5132799: potential clinical application in rational combination with molecular targeted therapeutics

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Background: The phosphatidylinositol 3-kinase (PI3K) pathway regulates various cellular processes, such as proliferation and apoptosis. Class I PI3K is a heterodimer, consisting of a regulatory and a p110 catalytic subunit, which transduces signals from receptor tyrosine kinases (RTKs). One of four p110 isoforms, p110α is known to be actively mutated in various human cancers. CH5132799 is a potent class I PI3K inhibitor with a novel structure, which will be presented in an accompanying poster. We will also present data showing that PI3K pathway-activated tumors, particularly the PIK3CA-mutated tumors, are sensitive to CH5132799. Here, we describe the preclinical efficacy in combination with current standard therapeutics, including RTK-targeted drugs.
Results: The trastuzumab-insensitive breast cancer cell line KPL-4, which harbors Her2 amplification and PIK3CA mutation (H1047R), showed tumor regression by CH5132799 monotherapy. The combination of CH5132799 with trastuzumab induced remarkable antitumor efficacy, resulting in the disappearance of the xenografted tumors. This suggests that CH5132799 can overcome trastuzumab insensitivity in PIK3CA mutants through PI3K inhibition. With lapatinib, *in vitro* cell growth inhibition and apoptosis was enhanced in Her2-amplified breast cancer BT-474 cells. Consistently, this combination enhanced tumor growth inhibition in the BT-474 xenograft model. These data indicate potent compatibility of CH5132799 with Her2-targeted drugs.
Combined administration of CH5132799 with erlotinib was also examined. In NSCLC NCI-H292 cells, erlotinib treatment suppressed EGFR-driven Erk phosphorylation with weak suppression of Akt phosphorylation, whereas CH5132799 could completely suppress Akt phosphorylation. When the drugs were combined, phosphorylation of Erk and Akt were efficiently suppressed concomitantly. Using this rationale, the combination of CH5132799 and erlotinib achieved enhanced antitumor efficacy in a H292 xenograft model.
In addition to RTK-targeted drugs, CH5132799 combined with paclitaxel induced more prolonged tumor growth inhibition than each alone.
Conclusions: CH5132799 showed enhanced efficacy when combined with current therapeutics including RTK-targeted drugs and paclitaxel. These results suggest potential clinical applications of CH5132799 in combination therapy with molecular targeted agents and cytotoxics. CH5132799 is progressing toward phase I clinical trials.

123 POSTER

Anti-tumor activity of CXR1002, a novel anti-cancer clinical phase compound that induces ER stress and inhibits PIM kinases: Human tumor xenograft efficacy and in vitro mode of action

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Summary: CXR1002 is an ammonium salt of perfluorooctanoic acid. It has a unique pharmacokinetic, pharmacologic and toxicity profile and induces cell death in a wide range of human tumor cells *in vitro* and *in vivo*. CXR1002 causes an ER stress response, acts as a fatty acid mimetic,