derivatives were obtained by changing the lipophilic or metoxy groups on the different positions of the phenyl ring.
Results: The results showed all compounds are inserted into a hydrophobic pocket in the active site region of ABCB2. The ki values has confirmed a good hydrophobic interaction of the designed compounds. The most potent compound was found to have two Cl groups on Meta- positions of the phenyl ring. The orientation of this derivative in the active site of P-gp 3D model was examined by a docking experiment. The molecular modeling shows that the NO_2 substituent forms a hydrogen bond interaction with the H of THR318. These observations and experimental results provide a good explanation for the potent and selective activity of these compounds.
Conclusion: The interactions of DHP derivatives showed that they can be considered as possible MDR reversing agents. In order to achieve better potency, it is better to keep the main structure and alternatively change the phenyl ring with a heterocyclic ring (eg. isoxazole) and add a lipophilic group (eg. Cl) to heterocyclic ring in Ortho- or Meta- positions. We hope the results of the present study are useful for the design of more effective compounds against cancer.

31LBA LATE BREAKING ABSTRACT

β-arrestin-dependent signaling by IGF-1R regulates the Ras induced transformation of mammalian cells

H. Zheng[1], N. Natalishvili[1], C. Mateoiu[1], A. Girnita[1], L. Girnita[1].
[1]*Karolinska Institutet, Oncology Pathology, Stockholm, Sweden*

Background: The receptors tyrosine kinase (RTKs) is a related family of cell surface receptors with similar structural and functional characteristics. Among them, the insulin-like growth factor receptor (IGF-1R) is one of the most important players in cancer development. IGF-1R is responsible for the transformation and proliferation of malignant cells, in prevention of apoptosis and in maintenance of the malignant phenotype of tumor cells. IGF-1R expression is a requirement for transformation by oncogenes. Mouse embryo fibroblasts with a disruption of the IGF-IR genes (R− cells), have been found to be resistant to transformation by a variety of viral and cellular oncogenes, except v-src and a mutant of Gq13. Recently, we provide evidence that b-arrestin1, which is better known to be involved in the regulation of GPCR, serves as an adaptor to bring the oncoprotein MDM2 to the IGF-1R leading to both the ubiquitination of the receptor and activation of MAPK/ERK signaling pathway.
Here we aim to investigate whether the β-arrestins mediated signals of IGF-1R is necessary for tumor transformation.
Material and Methods: We used mouse embryonic fibroblast cells (MEF) lacking β-arrestin1 (KO cells) and control MEFs stably transfected either with H-RasV12 (MEF-Ras; KO-Ras), PyMT (MEF-MT; KO-MT) or v-Src (MEF-Src; KO-Src). The transfection efficiency was verified by Western blot. To evaluate transformation we tested the cells for proliferation under serum free conditions and the ability to form colonies during anchorage independent growth.
Results: Our results suggest that oncogenic H-Ras is unable to transform immortalized mouse embryonic fibroblasts in the absence of β-arrestin1. The direct explanation of H-Ras inability to transform cells devoid to beta-arrestin is the impaired IGF-1R signaling and insufficient activation of the PI3K/Akt and ERK pathways.
Conclusions: The present results propose a more generalized, alternative mechanism for transformation by Ras and, implicitly, another possible way for targeting Ras in tumor cells.

32LBA LATE BREAKING ABSTRACT

High level gene amplification of MYC characterizes radiation-induced angiosarcomas

P. Hohenberger[1], K. Mössinger[2], J. Manner[2], B. Radlwimmer[3], P. Lichter[3], R. Sciot[4], J.M. Coindre[5], D. Katenkamp[6], P. Ströbel[2].
[1]*Mannheim University Medical Centre, Division of Surgical Oncology and Thoracic Surgery, Mannheim, Germany;* [2]*Mannheim University Medical Centre, Department of Pathology, Mannheim, Germany;* [3]*German Cancer Research Center, Department of Molecular Genetics, Heidelberg, Germany;* [4]*University Hospital Gasthuisberg, Department of Pathology, Leuven, Belgium;* [5]*Institute Bergonie, Department of Pathology, Bordeaux, France;* [6]*Universitätsklinikum, Department of Pathology, Jena, Germany*

Angiosarcomas (AS) are rare vascular malignancies that arise either *de novo* as primary tumors or secondary to irradiation or less often to chronic lymph edema. The cytogenetics of angiosarcomas are poorly characterized.
We applied array-CGH as a screening method to identify and FISH to confirm recurrent alterations in 33 secondary angiosarcomas (31 tumors secondary to irradiation, 2 tumors secondary to chronic lymph edema) and compared the results with 28 primary angiosarcomas. Recurrent genetic alterations were identified only in secondary but not in primary cancers.
The most frequent alterations were high level amplifications on chromosome 8q24.21 (50%), 10p12.33 (33 %) and 5q35.3 (11 %). FISH analysis confirmed high level amplification of *c-myc* on chr. 8q24.21 as a recurrent genetic alteration found exclusively in AS secondary to irradiation or chronic lymph edema. Amplification of *c-myc* was not predisposing to high grade morphology or increased cell turn over.
In conclusion, in spite of their identical morphology, secondary AS are genetically different from primary AS and are characterized by a high frequency of high level amplifications of *c-myc*. These findings may have implications both for the diagnosis and treatment of these tumors. Therapeutics targeting MYC and MYC-dependent signalling could be of major interest.
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33LBA LATE BREAKING ABSTRACT

Synergistic augmentation of arsenic trioxide-induced cytotoxicity by BCNU through reactive oxygen species-related autophagic pathway in human solid tumors

C. Kuo[1], T. Liu[1], L. Chen[1], H. Shiah[1], W. Pan[1], J. Liu[1], Y. Cheng[1], J. Chang[1]. [1]*National Health Research Institutes, Institute of Cancer Research, Tainan, Taiwan*

Background: Arsenic trioxide (ATO) is an effective cancer therapeutic drug for acute promyelocytic leukemia and has potential anticancer activity against a wide range of solid tumors. To improve therapeutic efficacy of ATO in solid tumors, we systematically investigated the combinatory interaction of this drug with other chemotherapeutic agents.
Material and Methods: Growth inhibition was determined using the methylene blue staining method and MTT assay. Two agents were combined at equitoxic ratios based on the IC_{50} of each drug. Efficacy improvement was evaluated using isobologram at 50% inhibition level. Western blot, flow cytometry, immunohistochemistry, enzymatic activity assay were used to reveal molecular events of synergistic interaction of two drugs in this study.
Results: Isobologram analysis revealed that BCNU exhibited synergistic interaction with ATO in human nasopharyngeal carcinoma (HONE-1), melanoma (A2058), glioblastoma (BBTRG-05MG), colorectal carcinoma (HT-29), gastric carcinoma (TSGH), and non-small-cell lung carcinoma (H460). Annexin-V-propidium iodide binding, caspase 3 activity, and PARP cleavage assay indicated that combined ATO with BCNU did not induce cellular apoptosis. Instead, special biological staining with acridine orange and microtubule-associated protein 1 light chain 3, revealed ATO plus BCNU resulted in an increased percentage of autophagic cell death in HONE-1 cells compared to ATO alone. Further analysed indicates that the synergistic augmentation of the cytotoxicity trough autophagic cell death by ATO with BCNU majority through the depletion of reduced glutathione followed augmentation of reactive oxygen species (ROS). Moreover, depletion of reduced glutathione is through the inhibition of catalytic activity of thioredoxin reductase and glutathione reductase.
Conclusion: Taken together, the synergistic interaction of ATO with BCNU is through ROS related-autophagic pathway. These findings will be useful in designing future clinical trial of combination chemotherapy with ATO and BCNU with a potential for a broad use against human cancers.

34LBA LATE BREAKING ABSTRACT

Activated cPLA2a correlates with HER2 over-expression and mediates estrogen-induced cell growth of breast cancer cells

F. Caiazza[1], A. Hill[2], L. Young[2], B.J. Harvey[1], W. Thomas[1]. [1]*Royal College of Surgeons, Molecular Medicine, Dublin, Ireland;* [2]*Royal College of Surgeons, Surgery, Dublin, Ireland*

The cytosolic phospholipase A2 (cPLA2α) catalyzes the hydrolisis of membrane glycerophospholipids to release arachidonic acid, which is converted to biactive eicosanoid lipid mediators, including prostaglandins produced through cycloxigenases, promoting activation of downstream proliferative cell signaling pathways. The eicosanoid signalling pathway contributes to cell proliferation in breast cancer. Numerous studies demonstrated a crucial role of COX-2 and PGE2 in breast tumorigenesis and progression. The specific role of cPLA2α, however, is not established. Recent work from our group demonstrated that 17β-estradiol (E2) can rapidly activate cPLA2α in the breast cancer-derived MCF-7 cell line, leading to the hypothesis that the rapid release of bioactive lipids may play a role in the proliferative signalling responses stimulated by E2 in breast cancer cells. We have shown that the E2-induced rapid activation of cPLA2α was dependent on specific trans-activation of EGFR/HER2