855 **Lack of protective effect by hypoxia on alpha particle radiation from radium-223**

H. Heier-Baardson[1], M. Dornish[1]. [1]*FMC BioPolymer AS, NovaMatrix, Sandvika, Norway*

The protective effect induced by reduced oxygen tension against radiation-induced cytotoxicity is well known. However, alpha particle radiation has been described as not responding to classical oxygen enhancement. Therefore, we wanted to document if reduced oxygen conditions (4% O_2) would affect *in vitro* cytotoxicity induced by the new alpha pharmaceutical Alpharadin (radium-223 chloride) relative to an oxygenated (20% O_2) atmosphere.
Radium-223 (Alpharadin) is in clinical phase 3 testing for improvement in survival of patients with bone metastases from prostate cancer and was provided by Algeta ASA, Oslo, Norway. NHIK 3025 cells, a cervical carcinoma cell line, were grown as monolayers under atmospheric oxygen (20% O_2) or cells were grown for 6 months under continuous hypoxic conditions at 4% O_2 and 5% CO_2. The desired radioactive concentration (kBq/ml) of Alpharadin (radium-223) was made by diluting the drug in cell culture medium. Treatment of single cells at various dose-rates was carried out either in 20% or 4% oxygen concentrations. For treatment under hypoxic conditions, all procedures including preparation of radium-containing medium, cell trypsinization, and exposure to radium-223 were carried out under 4% O_2. Cytotoxicity was determined by counting colonies from surviving cells. The radioactive dose was recalculated to express the cellular dose.
The data show that the cell survival curve of cells treated at atmospheric oxygen (20% O_2) had a form described by the Linear-Quadratic Model, $S = \exp;(\alpha D + \beta D2)$, with a α-value of 3.8 and a β-value of 0.4, essentially describing a log-linear relationship between cellular dose of radioactivity and cell survival. When cells that were continuously cultured under 4% O_2 (i.e. a chronic state of hypoxia) were treated with radium-223, the number of surviving cells was similar to that found when cells were treated under atmospheric oxygen. There is apparently no protective effect of reduced oxygen concentration on radium-223-induced cytotoxicity.
These data can be interpreted to indicate that Alpharadin (radium-223) induces similar cytotoxic effects irrespective of oxygen concentration. Combined with the bone-targeting potential of Alpharadin, these data support the use of radium-223 in clinical settings where tumours may have areas of reduced oxygen concentration.
This work has been funded with the support from METOXIA project no.222741 under the 7th Research Framework Programme of the European Union.

856 **Chemotherapy of locally advanced nasopharyngeal carcinoma**

L. Bolotina[1], A. Kornietskaya[1]. [1]*Moscow Research Institute of Oncology name of P.A. Hertzen, Chemotherapy, Moscow, Russian Federation*

Background: To evaluate efficiency of induction chemotherapy for treatment of locally advanced nasopharyngeal carcinoma.
Materials and Methods: 40 pts (27 males, 13 females), age 20−77 years (mediana 42 years). Undifferentiated nasopharyngeal carcinoma was diagnosed in 26 pat, low differentiated squamous cancer in 14 patients. T2N1−3/0 – 7 pts, T3N0−2/0 – 2 pts, T4N0/0 – 19 and T4N1−3/0 – 12 pts. Treatment regimen: docetaxel 75 mg/m2 – 1 day, cisplatin 75 mg/m2 – 1 day, doxorubicin 45 mg/m2 – 1 day. Interval between cycle was 21 days. Altogether 227 maintenance chemotherapy courses were carried out (from 2 to 4 courses – 5 pts, 6 – 17 pts, 8 courses – 17 and 13 pts, 5 pts are still being treated). The efficiency was evaluated based on the CT and MRI, endoscopic and ultrasound examinations, and biopsy following every even-numbered course.
Results: Overall response (RECIST) was 72.5% – 29 patients (CR 47.5% – 19 pts including those referred to T4N2, PR was in 10 pts – 25%). After of the chemotherapy all the patients were subjected to radiotherapy, and if positive lymph nodes were found out in the neck, they were subjected to lymphadenectomy. Stabilization of disease 3 (7.5%) and inefficiency of chemotherapy at 2(5%) pts, accordingly. One patient, 77 years, was excluded from the study because of severe toxicity development. Progression-free survival rates were: 12 months – 7 pts, 12−24 months – 4 pts, more then 24 months – 4. Disease-free survival is 17 patients, the maximum period of follow-up in this group 68 months (median 21.8).
Conclusion: This trial demonstrated the significant efficiency of induction chemotherapy in the first stage of a combination therapy on patients with locally advanced nasopharyngeal carcinoma.

Tuesday 29 June 2010 09:45−17:30

Poster Session
Carcinogenesis

857 **Role of MKP1 in skin carcinogenesis**

V. Rodriguez Fanjul[1], S. Zazo[2], I. Sanchez-Perez[1], F. Rojo[2], R. Perona[1]. [1]*Biomedical Research Institute, Departamento de Modelos Experimentales de Enfermedades Humanas, Madrid, Spain,* [2]*Fundación Jiménez Díaz, Servicio de Anatomía Patológica, Madrid, Spain*

Dual-specificity phosphatase type 1 (DUSP1/MKP1), is a member of the dual-specific family of phosphatases that can dephosphorylate and inactivate all three major Mitogen-Activated Protein Kinases (MAPKs), including Extracellular Regulated Kinase (ERK1/2), c-Jun N-Terminal Kinase (JNK), and p38. MKP1 is a nuclear protein whose expression is regulated by mitogenic, inflammatory and DNA damage stimuli. Basal levels of MKP1 are usually low in normal cells, however high levels of the protein have been found in several human tumours such as ovarian, breast, prostate and lung. Amplification and mutation of Ha-ras correlates with the malignancy of tumours that appears in chemically-induced mouse skin and additionally, an increase in Ha-ras levels induces JNK and ERK activity, known substrates of MKP1. The objective of this study was to investigate the role of MKP1 in skin cancer. MKP1 wild-type (WT) and MKP1 knock-out (KO) mice were subjected to the standard two-stage skin carcinogenesis protocol using 7, 12-dimethylbenz(a)anthraacene (DMBA) as the initiator and 12-O-tetradecanoylphorbol-13-acetate (TPA) as the promoter. We observed a significant decrease in both papilloma incidence and papilloma multiplicity in WT mice undergoing two-stage skin carcinogenesis relative to KO littermates. Morphological evaluation of skin lesions from MKP1 WT and KO mice revealed a significant reduction in both tumour incidence and tumour multiplicity in WT mice relative to KO littermates. No differences were found between MKP1 WT and MKP1 KO skin hyperplasia following TPA challenge, but we observed reduced bromodeoxyuridine **(**BrdUrd) incorporation in MKP1 WT epidermis compared with MKP1 KO epidermis. Targeted disruption of MKP1 gene led to a lightly increase of ERK1/2 protein in MKP1 KO mice, whereas p38 and JNK1/2 proteins were expressed at similar levels in the epidermis of MKP1 WT and MKP1 KO mice. We examined the effect of MKP1 deficiency on ERK1/2 activation and we observed that TPA-mediated activation of ERK1/2 was diminished in MKP1 WT epidermis compared with KO epidermis. Contrary to the results in other tumours as lung cancer, our data suggest that MKP1 expression plays a protective role in skin carcinogenesis by attenuating epidermal response to tumour promotion, and ultimately, two-stage skin carcinogenesis, very likely by impairing the activation of the ERK1/2 pathway, critically linked to control of cell proliferation and skin tumourigenesis.

858 **Deficiency of Notch2 suppresses pancreatic carcinogenesis and Myc signaling in vivo**

P.K. Mazur[1], B. Sipos[2], U. Zimber-Strobl[3], L.J. Strobl[3], F. Radtke[4], R.M. Schmid[1], J.T. Siveke[1]. [1]*Klinikum rechts der Isar, Technische Universität München, Internal Medicine, München, Germany*, [2]*University Hospital Tübingen, Department of Pathology, Tübingen, Germany,* [3]*Helmholtz Center Munich, Department of Gene Vectors, München, Germany,* [4]*Ecole Polytechnique Federale de Lausanne, SV/ISREC, Lausanne, Switzerland*

Notch signaling is a key regulator of cell fate specification and its dysregulation often occurs in tumour development including pancreatic cancer. Given the astonishing plasticity of pancreatic exocrine cells and the resistance of most cells to oncogenic $Kras^{G12D}$-induced transformation, we suggested Notch signaling being of integral importance in early neoplastic transformation. Here we demonstrate the effect of pancreas-specific Notch receptor ablation in oncogenic $Kras^{G12D}$-driven carcinogenesis. Expression analysis revealed predominant expression of Notch1 in acinar and Notch2 in duct and centroacinar cells. We show that deficiency of *Notch2* but not *Notch1* leads to an increased survival, a progression stop at the PanIN1 level, and increased development of lesions resembling mucinous cystic neoplasms. Malignant transformation occurred late with a shift in tumour cell differentiation towards anaplastic cancers with an increased rate of epithelial-mesenchymal transition (EMT). Expression profiling identified suppression of Myc signaling in *Notch2*-deficient pancreata and pancreatic cancer caused by transcriptional regulation of Myc by Notch2. Our data place Notch2 as a central regulator during PanIN progression and malignant transformation through modulation of Myc signaling and EMT.