Material and Methods: The study included 150 postmenopausal breast cancer patients with detectable levels of steroid receptors (ER+PR+) that should indicate hormone dependent disease. IL-8 and MMP-9 levels were determined by ELISA in primary tumor tissue lysates.
Results: There was a strong positive correlation between IL-8 and MMP-9 expression (Spearman rank order test, $p < 0.001$). Furthermore, MMP-9 expression was significantly higher in patients with higher levels of IL-8 according to median IL-8 level (M = 28.42 pg/mg) and IL-8 expression was significantly higher in patients with higher levels of MMP-9 (M = 1.87 ng/mg, Mann–Whitney rank sum test, $p = 0.05$ and $p = 0.008$, respectively). There was a significant negative correlation between ER and IL-8, as well as between PR and IL-8 expression (Spearman rank order test, $p = 0.02$ and 0.006, respectively). There was no statistically significant correlation between ER and MMP-9 expression, neither between PR and MMP-9.
Conclusions: Positive feedback loop between IL-8 and MMP-9 might be mechanism of promotion of angiogenesis and progression of hormone dependent breast cancer.
No conflict of interest.

108 Potential effects of telomerase activity and Bcl-2 expression on the apoptosis of the human brain tumors

C. Kim[1], J.H. Cheong[1], J.M. Kim[1]. [1]*Hanyang University Hospital, Department of Neurosurgery, Seoul, Korea*

Background: Apoptosis is regulated by several gene products including Bcl-2, which has been known to be anti-apoptotic property. Additionally, telomerase, a ribonucleoprotein that synthesizes telomeres, has been identified in various human neoplasms and its potential roles should be clarified. In the present study, we investigated the apoptotic effect of Bcl-2 and telomerase activity in the surgical specimens of human brain tumors.
Material and Methods: A total of 76 cases of surgically resected brain tumors were included in this study. Telomerase activity was examined by the telomeric repeat amplification protocol assay, and Bcl-2 was characterized by the Western blot analysis. Apoptosis of the specimens was detected by DNA fragmentation analysis.
Results: Telomerase activity was detected in 65.8% (50/76) of the brain tumors, which induced apoptosis in 20.0% (10/50). Bcl-2 was also expressed in 23.7% (18/76) of the brain tumors, which induced apoptosis in 11.1% (2/18). In 14 cases with Bcl-2 expression and negative telomerase activity, apoptosis was detected in 21.4% (3/14). However, apoptosis was not induced in all 4 cases with Bcl-2 expression and positive telomerase activity. These results suggested that apoptosis was enhanced in the brain tumors with Bcl-2 expression and negative telomerase activity ($p < 0.05$). In the 24 cases without Bcl-2 expression and telomerase activity, apoptosis was found in 25% (6/24). Apoptosis was induced in 23.4% (8/34) of brain tumors, which Bcl-2 was not expressed and telomerase activity was positive. Their difference was not significant statistically.
Conclusions: Our results suggest that apoptosis of the human brain tumors with Bcl-2 expression may be influenced by telomerase activity, however, telomerase activity may not affect on apoptosis of the human brain tumors without Bcl-2 expression. These indicate that telomerase activity may have a dependent effect on apoptosis of the human brain tumors.
No conflict of interest.

110 Biological activity of novel platinum(II)–iodido complexes

L. Filipovic[1], A. Savic[2], S. Arandjelovic[1], T. Sabo[2], S. Grguric-Sipka[2], S. Radulovic[1]. [1]*Institute of Oncology & Radiology of Serbia, Department of Experimental Oncology, Belgrade, Serbia,* [2]*University of Belgrade, Faculty of Chemistry, Belgrade, Serbia*

Introduction: Novel platinum(II)–iodido complexes of general formula $[PtI_2(L^{1-3})]$, (complexes **C1**–**C3**, ligands **L1**–**L3**): where L^{1-3} are isobutyl, *n*-pentyl and isopentyl esters of (*S,S*)-propylenediamine-*N,N′*-di-2-(3-cyclohexyl)propanoic acid have been synthesized and characterized by elemental analysis, UV/Vis, IR, NMR spectroscopy and mass spectrometry, in order to investigate their biological activity and to elucidate the mechanism of action. All studies were performed in comparison to cisplatin.
Material and Method: The cytotoxic activity of the complexes **C1**–**C3** and ligands **L1**–**L3** was investigated by MTT assay for 48 h of continual action on four tumor cell lines HeLa, LS-174, MDA-MB-231; one transformed endothelial cell line EA.hy 926; and one normal MRC-5 cell line. Quantitative analysis of cell cycle phase distribution was performed by flow-cytometric analysis of the DNA content in fixed HeLa cells, after staining with propidium iodide. Analyses of the mode of cell death were performed using flow cytometry by Annexin-V-FITC assay, and fluorescence microscopy.
Results and Discussion: Complexes **C1**–**C3** exhibited activity comparable to cisplatin, with the highest potential in HeLa, LS-174 and EA.hy 926 cells. Precursor ligands (**L1**–**L3**) showed approximately two- to four-times less activity comparing to the corresponding complexes irrelevant to the target cell line, with the highest activity observed in EA.hy 926. MRC-5 and A549 cells were the least sensitive to the action of complexes and ligands. **C1**–**C3** induced apoptotic changes characterized by externalization of phosphatidylserine, generation of considerable sub-G1 peak and some apoptotic morphological alteration. Only **C1** showed higher potential for apoptosis induction in comparison to the precursor **L1** and cisplatin.
Conclusion: Structure-activity comparison in this study revealed that co-ordination of (*S,S*)-propylenediamine-*N,N′*-di-2-(3-cyclohexyl)propanoic acid esters to platinum(II) metal center resulted in increased cytotoxicity of complexes, comparing to precursor ligands. Cytotoxic activity of **C1**–**C3**, was comparable or higher to those observed for cisplatin. Analyses of the mode of cell death by flow cytometry and fluorescence microscopy, suggested different mechanism of action of novel iodido-platinum complexes compared to cisplatin. Altogether novel iodide-platinum complexes showed promising biological activity and their potential in cisplatin resistant cell lines should be further investigated.
No conflict of interest.

111 RANK pathway as a new therapeutic target in primary breast cancer

P. Pellegrini[1], A. Cordero[1], E. González-Suarez[1]. [1]*Biomedical Research Institute IDIBELL, Cancer Epigenetics and Biology Program, L'Hospitalet de LLobregat, Spain*

Background: RANK is a key pathway of mammary gland differentiation and mediates progesterone induced mammary tumorigenesis in mice. However, the therapeutic impact of targeting RANK signaling in established tumors is unknown.
Materials and Methods: Expression profile of RANK and RANKL was characterized by quantitative PCR and immunohistochemistry in MMTV-neu and MMTV-PyMT normal tissues and tumors. For primary cultures, tumors were plated in 3D matrigel cultures and RANK signaling was stimulated with RANKL. For *in-vivo* assays 3D colonies where dispersed into single cells and injected in mammary glands (tumor growth assays) or tail vein (metastasis assays) of immunodeficient mice.
Results: RANK is highly expressed in tumors of two widely used models of spontaneous mammary tumorigenesis: MMTV-neu and MMTV-PyMT. Stimulation of RANK signaling by RANKL in cells derived from MMTV-neu and MMTV-PyMT carcinomas promotes cell proliferation, survival and increased tumor growth rate. In addition, RANKL treatment results in increased invasion of tumor cells and increased metastasis formation ability.
Conclusions: RANK signaling plays an important role in mammary tumor progression and targeting RANK may be beneficial for breast cancer therapy.
No conflict of interest.

113 Expression of voltage-gated sodium channel beta1 subunits in breast cancer: Promotion of tumor growth and metastasis

M. Nelson[1], R. Millican-Slater[2], L.C. Forrest[1], W. Brackenbury[1]. [1]*University of York, Department of Biology, York, United Kingdom,* [2]*St James's University Hospital, Department of Histopathology, Leeds, United Kingdom*

Introduction: Voltage-gated Na^+ channels (VGSCs) are heteromeric proteins composed of pore-forming alpha subunits and smaller beta subunits. The beta subunits are channel modulators and are also cell adhesion molecules (CAMs). Beta1, encoded by *SCN1B*, is best characterized in the central nervous system (CNS), where it regulates electrical excitability, neurite outgrowth and migration during development. Beta1 is also expressed in breast cancer cell lines, where it regulates adhesion and migration *in vitro*. Here, we show that beta1 plays a functional role as a CAM in regulating tumour growth and metastasis.
Materials and Methods: We studied beta1 expression using Oncomine and immunohistochemical analysis of patient tissue specimens. We investigated the effects of beta1 on tumour growth and metastasis by orthotopic injection of MDA-MB-231 cells into mice, followed bioluminescent imaging, immunohistochemistry and confocal microscopy. The effect of beta1 on process outgrowth was assessed by immunocytochemical analysis of breast cancer cells grown on fibroblast monolayers.
Results: *SCN1B* mRNA and beta1 protein were up-regulated in breast tumours, compared with normal tissue. Over-expression of beta1 in MDA-MB-231 cells increased tumor growth and metastasis in a xenograft model of breast cancer. Beta1 overexpression also increased VEGF secretion and vascularisation, but reduced apoptosis. Beta1 potentiated outgrowth of neurite-like processes from breast cancer cells cultured with fibroblasts. Process outgrowth in breast cancer cells specifically required the extracellular adhesion domain of beta1. Beta1-mediated process outgrowth also required Na^+ current and fyn kinase activity.
Conclusions: Beta1-mediated process outgrowth in breast cancer cells recapitulates the mechanism by which beta1 regulates neurite outgrowth in CNS neurons. We conclude that when present in breast tumors, beta1 enhances pathological growth and cellular dissemination by recapitulating