regardless their molecular mechanisms. Furthermore, we found the positive linear relationship between relative activity of AKT and ERK1/2 combined and cell viability as r = 0.948 in the same manner. The results obtained suggest quantitative cross-talk between the main two pathways regardless molecular mechanisms, which may aid cancer drug selection to a patient.

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Human papillomavirus (HPV) infection, p53 overexpression and histopathologic factors in colorectal cancer

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Background: There is evidence of a possible etiological role of human papillomaviruses (HPVs) in the development of colorectal cancer. Loss of p53 tumor suppressor gene function has been found in many malignancies and it can occur in a variety of ways, including gene mutation and interaction with the E6 protein of oncogenic human papillomaviruses (HPVs). The aim of this study was to verify the prevalence of HPV infection and p53 overexprssion in colorectal cancer tissue samples and its association with histopathologic factor.
Materials and Methods: Sixty tissue sections from CRC patients were investigated immunocytochemically for aberrant expression of p53 using the streptavidin-biotin-peroxidase method with monoclonal antibodies. HPVstatus was also analyzed using type-specific primers for HPV16/18 by polymerase chain reaction (PCR).
Results: Overall, 21of 60 patients (35%) presented HPV DNA; HPV 18 was detected in 19of 60 samples (31.7%) and HPV16 in 11 of 60 (18.3%). An abnormal expression of tumor-suppressor protein p53 were observed in 29 0f 60 (48.3%) samples. P53 overexpression was observed in 15/21 (71.4%) of HPV positive and 14/39 (35.8%) of HPV negative patients (P = 0.009). Same significant difference were found between HPV18 and p53 (P = 0.007) but not in HPV16 (P = 0.261). HPV DNA presentation was not significantly associated with histopathologic factor including tumor stage (P = 0.428), grade (P = 0.668), PNI (P = 0.265) and LVI (P = 0.275).
Conclusion: Our results suggest that p53 inactivation caused by HPV infection may play a role in the pathogenesis of colorectal cancer but there is not any association between HPV infection with histopathologic factor.

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Effects of cisplatin exposure on the expression of Bcl-2-family proteins: differences between cisplatin-sensitive and -resistant malignant pleural mesothelioma cells

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Background: Resistance toward apoptosis is one of the hallmarks of cancer, and cancer therapy failure is often attributed to apoptosis resistance. Malignant mesotheliomas (MM) are aggressive tumors that frequently acquire drug resistance during treatment. The chemotherapy regimens available often include the chemotherapeutic drug cis-diamminedichloroplatinum(II) (cisplatin, CDDP). In MM, there is evidence that the apoptosis-resistant phenotype is a consequence of suppressed mitochondrial membrane permeabilisation (MMP). The Bcl-2 family of proteins, which includes both pro-apoptotic proteins (e.g. Bim, Puma, Bid, Bad, Bmf) and pro-survival proteins (e.g. Bcl-2, Bcl-XL), is essential for the regulation of the MMP. We compared a malignant pleural mesothelioma cell line (P31wt) with its CDDP-resistant sub-line (P31res) regarding CDDP effects on the expression of Bcl-2-family proteins.
Materials and Methods: After 0.5, 2 or 6 h CDDP exposure, protein expression in cell lysates was determined with Western blotting. Equitoxic concentrations, 10 mg/L (P31wt) and 40 mg/L (P31res), of CDDP were used: 72 h after a 6-h exposure to CDDP, 50% of the cells had died of apoptosis, as determined by TUNEL staining.
Results: Under control conditions, some proteins were differently expressed: (1) the P31res cells did not express the most potent isoform of Bim; (2) P31res cells had a reduced expression of Puma; and (3) the P31res cells had a higher expression of P-Bcl-2 and P-Bad. In P31wt cells, which have a primary resistance toward CDDP compared to many other cancer cell lines, CDDP exposure (1) increased the expression of Bim and Puma, (2) increased the expression of Bad, and (3) decreased the expression of Bcl-2. In P31res cells, which have an acquired resistance toward CDDP, CDDP exposure (1) increased the expression of Puma, (2) decreased the expression of P-Bad, and (3) decreased the expression of pro-survival Bcl-2 and Bcl-XL.
Conclusions: Compared to P31wt, the P31res cells had lower expression of potent pro-apoptotic proteins and higher expression of P-Bad and P-Bcl-2. Cisplatin exposure reduced the expression of pro-survival proteins in both cell lines, but the effect on pro-apoptotic proteins differed: in P31wt most of the pro-apoptotic proteins increased, in P31res cells only Puma expression increased. These results suggest that the regulation of pro-apoptotic proteins can have an important role in CDDP resistance.

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Clinical requirements of "In Silico Oncology" as part of the integrated project ACGT (Advancing Clinico-Genomic Trials on Cancer)

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Background: New methods and technologies in molecular biology will result in an exponential increase of information that can be handled by the advances of high-computing and informatics. It is of paramount importance to gather this information with clinical data to gain new knowledge for developing better and more individualized treatments for cancer patients. This approach results in clinico-genomic trials, as ACGT (Advancing Clinico-Genomic Trials on Cancer) is running.
Materials and Methods: Substantial efforts have been made in mathematically simulating tumour growth and response to treatment resulting in a discipline called In Silico Oncology. Such in silico experiments might help clinicians to find the best way of treating an individual patient by simulating different treatments in the computer before starting the treatment in reality.
Results: From a clinical point of view two preconditions are of utmost importance, before a physician can rely on predictions of in silico simulations:
1. every in silico experiment has to be part of a clinico-genomic trial
2. every prediction of an in silico experiment has to be compared with the reality.

In the process of developing in silico experiments it is necessary to define the necessary and available data in a first step, including data from the tumor (molecular biology, pathology, imaging), from the patient (clinical data) and from possible treatments (pharmacokinetics of drugs, the treatment schema). Because the amount of data is restricted by the availability of tumour material, imaging data and clinical data, In Silico Oncology has to be part of clinico-genomic trials based on GCP criteria.
The simulation prediction of each in silico experiment has always to be compared with the reality. Only if there are no or minimal deviations between the prediction and the reality the in silico experiment is allowed to be used in a clinical setting. Before an in silico experiment can be accepted as a routine method for treatment stratification, a prospective and randomised trial has to show that patients treated according to the result of the in silico simulation experiment do better, than those treated regardless of the result.
Conclusions: In ACGT in silico models of breast cancer and nephroblastoma are tested regarding tumour growth and response to treatment.
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Analysis of coding and non-coding regions of thymidylate synthase gene in colorectal cancer patients and its possible relationship with 5-fluorouracil drug response

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Background: Thymidylate synthase (TS) catalyzes methylation of dUMP to dTMP and is the target of 5-fluorouracil (5-Fu). TS gene has regulatory tandemly repeated sequences in its 5′ and 3′ untraslated regions (5′-3′ UTR). TS levels vary considerably among tumors and the response to 5-FU is influenced by the intratumoral activity of the enzyme, with high levels generally being associated with a poor response. A recently detected 6 bp deletion polymorphism in the 3′UTR of the TS gene might also