

gene in 3/4 tests. In a cross validation of this gene in cell line and xenograft datasets, its overall predictive accuracy was 77% and 86% respectively.  
**Conclusions:** UPB1 and CTPS2 are promising novel candidate determinants of 5-FU activity. On-going studies are incorporating gene combination analyses, and gene modulation and human tissue investigations.

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#### Genetic polymorphisms associated with adverse events in childhood acute lymphoblastic leukaemia treated with SHOP-2005 protocol

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Acute lymphoblastic leukaemia (ALL) is the most common childhood cancer, and still the most important cause of cancer-related death in children. Although the introduction of treatment protocols has improved survival, interindividual differences in drug responses are an important cause of resistance to treatment and adverse drug reactions. Pharmacogenetic studies are providing a rational base for further treatment efficacy and reduction of complications.

The aim of the present study was to determine if there was a correlation between genetic polymorphisms and toxicity and/or outcome during therapy in paediatric ALL patients treated according to the SHOP-2005 protocol (high-dose methotrexate [MTX] and 6-mercaptopurine [6-MP]).

We analyzed 12 polymorphisms of 9 genes in 21 paediatric ALL patients: 3 genes of the MTX pathway (MTHFR, RFC1 and ABCB1), 1 gene of the 6-MP pathway (TPMT) and 5 genes involved in xenobiotic detoxification (CYP1A1, NQO1 and the GSTs GSTM1, GSTT1 and GSTP1). Then, data were analyzed by using the Fischer exact test.

Several associations were found, such as that of the MTHFR C677T and A1298C polymorphisms and minimal residual disease (predictor of relapse in ALL), and the association between the MTHFR A1298C polymorphism and vomiting, as well as that of the GSTM1 null genotype and diarrhoea. Moreover, when the genes involved in the MTX pathway and the GST genotypes were analyzed together, they predicted diarrhoea even better than GSTM1 alone.

Our results indicate that several polymorphisms of the MTX-related genes and GST genes may be useful as predictors of gastrointestinal toxicity and outcome of the SHOP-2005 treatment protocol.

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#### Influence of PXR haplotype variants on paclitaxel pharmacokinetics and pharmacodynamics in Asian cancer patients

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**Background:** Paclitaxel is primarily metabolized by CYP3A4 and CYP2C8 and transported by ABCB1, which are downstream targets of the pregnane X receptor (PXR) gene. The objective of this exploratory study was to investigate the influence of PXR genetic variants on the pharmacokinetics and pharmacodynamics of paclitaxel in Asian cancer patients.

**Materials and Methods:** A total of 25 Asian cancer patients receiving intravenous infusions of paclitaxel either as a weekly (80 mg/m<sup>2</sup>, N = 11) or three weekly (170 mg/m<sup>2</sup>, N = 14) dosage regimens were recruited. Pharmacogenetic and pharmacokinetic data were available for all the patients and pharmacodynamic data was available for 12 patients. Paclitaxel pharmacokinetic parameters were estimated using non-compartmental analysis (WinNonlin) and Mann-Whitney U test was used to assess genotypic-phenotypic correlations.

**Results:** Two main PXR haplotype groups were identified, PXR\*1B and non-PXR\*1B haplotype groups. The PXR\*1B haplotype group was tagged by the IVS6-17C>T and 2654T>C SNPs. Patients harbouring the PXR\*1B haplotype constitution had significantly lower clearance [CL/dose (mL × h<sup>-1</sup> × mg<sup>-1</sup>), median: 94.0; range: 45.3–207.2] and significantly higher exposure levels of paclitaxel [AUC<sub>0-∞</sub>/dose (hr × μg × mL<sup>-1</sup>): median: 52.8; range: 35.5–89.0] compared to patients belonging to the non-PXR\*1B haplotype group [CL/dose (mL × h<sup>-1</sup> × mg<sup>-1</sup>), median: 229.50; range: 65.5–624.3, (P = 0.03) and AUC<sub>0-∞</sub>/dose (hr × μg × mL<sup>-1</sup>): median: 27.2; range: 12.5–53.9, (P = 0.007), respectively]. Patients carrying the PXR\*1B haplotype group also had significantly higher C<sub>max</sub> levels of paclitaxel

[C<sub>max</sub>/dose (μg × mL<sup>-1</sup>): median: 17.6; range: 12.1–40.9] compared to patients belonging to the non-PXR\*1B [C<sub>max</sub>/dose (μg × mL<sup>-1</sup>): median: 11.03; range: 1.3–22.5, P = 0.03] haplotype group. Pharmacodynamic analysis revealed that patients carrying the PXR\*1B haplotypic constitution had 2.1- and 1.7-fold lower absolute neutrophil counts and platelet counts when compared to the patients bearing the non-PXR\*1B haplotypic constitution.

**Conclusion:** The PXR\*1B haplotype group was found to be associated with significant alterations in the pharmacokinetics of paclitaxel and a non-significant trend towards decreased ANC counts and thrombocytopenia. This exploratory study suggests that PXR haplotype constitution may be important in influencing interindividual variations in the disposition of paclitaxel.

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#### Transcriptome analysis method for in vivo mechanism of action study: IMC-D11 anti-FGFR3 +/- cisplatin in bladder cancer models

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**Background:** IMC-D11, a fully human IgG1 against the human fibroblast growth factor 3 (FGFR3), enhances the anti-tumor effects of cisplatin (CDDP) when given as a combination therapy in the RT112, RT4 and BFTC-905 bladder cancer xenograft models. The molecular mechanisms in support of this combination however have not been fully elucidated. To this end, we took a systems approach to gain further insights into the molecular networks underlying the synergistic/additive effects between IMC-D11 and CDDP in vivo.

**Materials and Methods:** Total RNA from RT112, RT4 and BFTC-905 derived tumors treated with IMC-D11, CDDP or the combination (n = 3 tumors per group) were subjected to a global gene expression profiling using Affymetrix Human Genome U133A array.

**Results:** The raw data were normalized, filtered and statistically analyzed, and the lists of genes significantly regulated by IMC-D11, CDDP or the combination treatment as compared to control groups were determined. Two levels of comprehensive bioinformatics analysis of these data were performed; at the gene level and at the pathway/network level. Combination treatment with IMC-D11 and CDDP uniquely altered the expression of many genes. In RT112 for example, DOK3, FOXP3 and hprt (1200 kb deletion mutant) were significantly upregulated only with combination treatment. However, none of the genes regulated by the combination treatment were found common to three models. We therefore further examined whether these differentially expressed genes are associated with common functions, networks, or processes using Gene Ontology (GO) annotation. The results indicate that the main GO classes found enriched in the combination group in the three models were related to the processes of cell cycle/proliferation, cell death/apoptosis, DNA replication and repair.

**Conclusions:** Results from these analyses, and others being performed, provide not only a molecular framework for further investigation on the mechanism by which IMC-D11 and CDDP exert their anti-tumor effects, but also crucial information that may potentially be utilized for optimizing therapeutic strategies against bladder cancer.

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#### In Mdm2 SNP309 cancer cells the small molecules nutlin-3 and MI-63 facilitate recruitment of RNA polymerase II to p53 target genes

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**Background:** Mdm2 inhibits p53 transactivation in part by forming a p53-Mdm2 complex on chromatin. A homozygous single nucleotide polymorphism (T to G) in the mdm2 gene at position 309 (SNP309) results in increased Mdm2 expression and increases susceptibility to cancer. In human cancer cells overexpressing Mdm2 due to homozygous G/G SNP309, the p53-Mdm2 chromatin complex is highly stable and is not disrupted following DNA damage.

**Materials and Methods:** To determine how the p53 response phenotype was influenced in cells with variable mdm2 genotypes using differential activation of the p53 pathway we compared targeted p53-Mdm2 complex disruption by the small molecule inhibitors Nutlin-3 and the MI-63 in wild-type p53 human cancer cell lines with variable SNP309 genotypes and wild type p53 to etoposide DNA damage treatment. The ability of the small molecule inhibitors to facilitate increased transcription factor recruitment to the chromatin was compared to the recruitment facilitated by treatment