DCM (by gavage or inhalation) or DCP +DCM (by gavage), and spontaneous tumours from vehicle/sham-exposed mice were analysed by whole-exome sequencing. Somatic mutation calling was performed to define exome-wide mutation patterns induced by DCP and DCM in these assays. Mutation data obtained in biliary tract cancers of workers in the printing industry who have been exposed to DCP and DCM as single agents or as mixtures, as well as with public somatic mutation data from biliary tract cancers were mined for the presence of the experimentally defined DCP and DCM mutational signatures.

Results and discussions Liver tumours from DCP and DCM exposed mice had distinct somatic mutations patterns compared to spontaneous liver tumours from vehicle/sham-exposed mice. While mutations in DCP-exposed mice were dominated by C:G>T:A transitions, the most frequent types of mutations in DCM-exposed mice were T:A>A:T and T:A>C:G substitutions. An average of 10.3 somatic mutations was observed per Mb in tumours from DCM-exposed mice, approximately 3-fold higher than in DCP-exposed or sham-treated mice. The mutation patterns found in DCP-exposed mice, but not DCM-exposed mice, presented some similarities with the mutational signature observed in cholangiocarcinomas of Japanese patients with occupational DCP/DCM exposure history.

Conclusion These results show that the analysis of tumour genomes from mouse carcinogenicity assays can support the characterisation of mutational signatures of carcinogenic compounds relevant to human exposures.

PO-320 GENE PANEL MUTATION SCREENING FOR A BETTER MOLECULAR STRATIFICATION OF COLORECTAL CANCER PATIENTS

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Introduction Colorectal carcinoma (CRC) is one of the most commonly diagnosed cancers worldwide. The metastatic disease contributes to the high mortality rate reported for such tumours. Significant benefit on overall survival was brought about the introduction of monoclonal antibodies anti-EGFR and anti-VEGF used in combination with chemotherapy in metastatic CRC (mCRC). While anti-VEGF treatment does not require biomarker-based selection criteria, the potential efficacy of anti-EGFR antibodies is neglected to patients with activating mutations in KRAS and NRAS (RAS) genes, whose molecular analysis became a clinical routine.

The advent of Next Generation Sequencing (NGS) instruments, able to reach quick testing of multiple clinically-relevant hotspots, yet maintaining precision and low costs, allows the simultaneous determination of the mutation status of an expanding number of genes. Despite only few of these molecular biomarkers have gained clinical utility in the routine oncological practice, the acquisition of more complex cancer mutational patterns may provide more efficient tumour characterisation for prognostic and predictive purposes and highlight actionable targets.

Material and methods We sequenced 639 mCRC samples by IT-PGM platform using a panel of hotspots and targeted regions of 22 genes (including RAS) commonly involved in CRCs. MSI analyses on 89 patients have been performed with a single fluorescent system comprising BAT25 and BAT26 mononucleotide repeats.

Results and discussions We identified recurrent mutations (≥1%) in 12/22 genes, being KRAS, TP53 and PIK3CA the most frequently mutated ones. Statistical analysis, indicated that the mutation associations follow a non-random distribution. Categorization of the cases on the base of KRAS and p53 mutation status led us the definition of 8 Mutation Association Patterns (MAPs) characterised by specific mutation associations. Analysis of the clinicopathological data available for 89 out of 639 cases indicates interesting trends for the associations of MAPs with specific parameters, some of which reached statistical significance.

Conclusion Application of NGS gene panel as a routine for the characterisation of RAS/BRAF status required for predictive purposes in CRC patients, may provide additional prognostic/predictive information, with no significant extra-costs.

PO-321 CAUSES AND CONSEQUENCES OF WDHD1 OVEREXPRESSION IN BREAST CANCER

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Introduction WDHD1 (WD repeat and HMG-box DNA binding protein 1) controls DNA replication, sister-chromatid cohesion and centromere integrity. These phenomena are often defective in breast cancer cells. This could lead to mutations, chromosomal aberrations and aneuploidy, which could promote breast cancer development and therapy resistance. This prompted us to investigate WDHD1 misexpression and its consequences in breast cancer.

Material and methods We performed systematic genomic, transcriptomic and proteomic analyses of WDHD1 expression in breast cancer using publicly available datasets, cell lines, primary cells and immunohistochemistry (IHC) on 547 invasive breast carcinomas with survival data up to 35 years post-diagnosis (Queensland Follow-Up resource). Functional studies included computational approaches, chromatin immunoprecipitations (ChIP), shRNA-mediated knockdown, various *in vitro* assays and *in vivo* xenograft modelling.

Results and discussions We find that WDHD1 mRNA and protein levels are significantly elevated in breast cancer. IHC identified WDHD1 as a novel prognostic marker. WDHD1 protein expression correlates strongly with grade, ER status, HER2 status, triple-negative status, lymphovascular invasion, lymphocytic infiltrate, central scarring or fibrosis, tumour border, Ki-67 expression and prognostic sub-groups. Somatic copy number gains contribute to WDHD1 overexpression, but more importantly, we establish that WDHD1 is an E2F target gene. Hence, defective RB pathway regulation directly promotes WDHD1 overexpression. Knockdown of WDHD1 decreases cell viability and proliferation, but it does not promote apoptosis. It increases genomic instability *in vitro* and reduces tumour growth in xenograft experiments.

Conclusion We identify WDHD1 mRNA and protein overexpression as novel markers for poor breast cancer prognosis.