polymorphisms and opioid dose, pain intensity, performance status, adverse effects, age, gender, bone or CNS metastases and breakthrough pain. Plasma concentrations of morphine and its major metabolites were determined by high performance liquid chromatography coupled with diode-array and electrochemical detectors.
Results: Genetic analysis showed that the polymorphisms OPRM1 A118G, COMT Val(108/158)Met and UGT2B7 C802T and T801A might influence the analgesic effect, with individuals GA, Val/Met and T801C802 being related with less morphine efficacy and high consumption. Also, differences in plasma concentrations of metabolites and metabolic ratios were found and correlated with the genetic variances.
Conclusions: These cases are consistent with the increasing evidence on the influence of polymorphisms in key molecules of nociception mechanisms, and in opioid receptors, transporters and metabolizing enzymes that can help us to understand the interindividual variability and lead to a patient-tailored treatment.

Understanding effects of Histone Deacetylase Inhibitors in Breast Cancer Epithelial-Mesenchymal Plasticity.

Pinto Cletus, Blick Tony, Lenburg Mark, Waltham Mark, Thompson Erik.

Despite significant progress in the detection and treatment of breast cancer, and a corresponding increase in breast cancer survival over the last decade, better diagnostic and therapeutic options are required for certain breast cancer subtypes (e.g. basal breast cancers), pre-existing metastases and patients that relapse. Patients with basal like breast cancer have severe metastasis and are associated with extremely poor prognosis. Analysis of basal like breast cancer cell lines revealed several similarities in gene profiles to cells that have undergone Epithelial-Mesenchymal Transition (EMT). EMT is widely accepted to provide tumour cells with the ability to migrate and invade secondary sites. The reverse process, Mesenchymal Epithelial Transition (MET), is then required to for establishment and proliferation of the malignant tumour cells.
Pharmacogenomic approaches using the Basal signature have been utilised to identify small molecule compounds specifically targeting cancer cells with Basal like expression profile. Using the Connectivity Map (Cmap) dataset (developed at the Broad Institute), we identified drugs capable to modulating expression of genes represented within the Basal signature. Preliminary data suggests that the HDACi may have upregulate genes associated with the basal phenotype. Current work revolves around validating these changes and assessing the role of HDACi as potential therapy for Basal BrCa in vitro.

Pharmacogenomic gene-drug relationships derived from in vitro model systems for drug lead discovery: case example sparc

Pinto Cletus, Blick Tony, Thompson Erik, Waltham Mark.

Since the early 90's, the US National Cancer Institute has screened >100,000 chemically defined compounds (plus natural product extracts) for growth inhibition properties towards 60 cancer cells lines. Cell lines included within this NCI60 cell screen include breast, renal, ovarian, leukemia, prostate, lung, colon and melanoma. 'Omic' profiling was initiated in the late 90's and a transcription profiling database for the NCI60 has now been established using both cDNA and Affymetrix microarrays. Patterns of compound potency can be mapped into the molecular characteristics (gene expression patterns) and our laboratories have used a number of bioinformatic programs to mine for drug leads towards specific gene products or cell line phenotypes. Here we describe the conceptual and experimental procedures undertaken to mine for leads against the gene product Secreted Protein Acidic and Rich in Cysteine (SPARC). SPARC is considered a good drug target in anticancer drug discovery given its roles in the tumour microenvironment and progression. From our studies, a family of related phenoxybenzylidenes and bleomycinamides structures were highly positively correlated with SPARC expression (Pearson correlation >0.5); indicating greater growth inhibitory activity by these compounds when SPARC is more abundantly expressed. These are regarded as lead drug structures that will be subsequently tested in appropriate isogenic cell culture systems which we have established in the laboratory

Pharmacogenomics of labour opioid analgesia: a systematic review.

Pinto Rute, Santos Marlene.

Interindividual variability in pain perception and sensitivity to analgesic therapy in labour is well described in the literature. Several factors account for this discrepancies, among these genetic variations. We aimed to systematically review and summarize the association of commonly studied single nucleotide polymorphisms (SNPs) with analgesic response in labour pain and to identify important gaps that remain for consideration in future studies. We performed a systematic review using studies identified in PubMed and ISI databases (from the date of the first available article to May 2012). Our review examined evidence of an association between genetic variations and opioids' analgesic response during labour. Of the 81 original papers, only 6 fulfilled the inclusion/exclusion criteria. Methodological quality was assessed with Downs&Back checklist. All the papers which address this issue are recent, and the oldest one dates from 2008 (Landau et al e Sia et al). Sample size ranged from 57 (Camorcia et al) to 676 women (Fatimah et al). The A118G (μ-Opioid receptor) polymorphism was the most reported one

to have an effect in labour analgesia. Most of the papers proved that A118G genetic polymorphisms interfere in labour epidural analgesia, and carriers of G118 allele seemed to be more sensitive to the opioid drugs (Landau et al) and require smaller dose (ED50) (Camorcia et al), even though there's no enough data to prove its interference in analgesia extent. However Sia et al (20) has shown that carriers of A118 allele are more sensitive to intravenous morphine administration. A118G polymorphism seems to influence variability in pain analgesia and side effects. However it seems to play a differential role whether the drugs are administered intravenously or via epidural route. Larger studies using validated methodology are required to fully elucidate the real effect of this polymorphism in labor pain.

Influence of common ABCB1 genetic polymorphisms in the risk of Major Depressive Disorder and antidepressant treatment phenotypes.

Santos Marlene, Carvalho Serafim, Lima Luís, Nogueira Augusto, Assis Joana Mota-Pereira Jorge, Pimentel Paulo Maia Dulce, Correira Diana, Gomes Sofia, Cru Agostinho, Medeiros Rui.

Major depressive disorder (MDD) is a highly prevalent disorder, which has been associated with an abnormal response of hypothalamus-pituitary-adrenal (HPA) axis. Reports have shown that abnormal HPA axis response can be due to an altered P-Glycoprotein (P-GP) function. This argument suggests that genetic polymorphisms in ABCB1 may have an effect HPA axis activity; however it is still not clear if this influences the risk of MDD. Moreover, there are reports that showed P-GP as responsible for the efflux of some antidepressant drugs; therefore ABCB1 genetic polymorphisms may influence treatment outcome. Our study aims to evaluate the effect of ABCB1 C1236T, G2677TA and C3435T genetic polymorphisms on MDD risk and antidepressant treatment phenotypes in a subset of Portuguese patients. DNA samples from 80 MDD patients of a 18 months-follow-up study carried at Hospital Magalhães Lemos, and 160 controls subjects were genotyped using TaqMan SNP Genotyping Assays. A significant protection for MDD males carrying T allele was observed (C1236T: OR=0.360, 95%CI:[0.140-0.950], p=0.022; C3435T: OR=0.306, 95%CI:[0.096-0.980], p=0.042; and G2677TA: OR=0.300, 95%CI:[0.100-0.870], p=0.013). Male Portuguese individuals carrying 1236T/2677T/3435T haplotype had nearly 70% less risk of developing MDD (OR=0.313, 95%CI:[0.118-0.832], p=0.016). No significant differences were observed regarding overall subjects. Regarding antidepressant treatment phenotypes, although no influence was found for each of the evaluated treatment phenotypes, specifically remission and treatment resistant depression, individuals carrying 1236TT display a shorter time to remission, and are likely to remit 7 weeks earlier that CC and CT carriers (Log rank test, p=0.045). Our results suggest that genetic variability of the ABCB1 is associated with MDD development in male Portuguese patients. The presence of 1236T/2677T/3435T haplotype affects P-GP activity and may influence HPA axis, due to an increased access of glucocorticoid into central nervous system (CNS). The observed gender-specific risk may be explained by a gender dimorphic sensitivity of the HPA-axis and reflect a gender-specific pathophysiology of depression. Regarding antidepressant treatment outcome, a putatively less active P-GP found among 1236TT genotype carriers, may lead to higher antidepressant concentrations in CNS, which explain the earlier remission.

FAS -670A>G genetic polymorphism is associated with Treatment Resistant

Santos Marlene, Carvalho Serafim, Lima Luis, Nogueira Augusto, Assis Joana, Mota-Pereira Jorge, Pimentel Paulo, Maia Dulce, Correia Diana, Gomes Sofia, Cruz Agostinho, Medeiros Rui.

Hippocampal neurogenesis has been suggested as a downstream event of the mechanism of action of antidepressants (AD) and might explain the lag time between AD administration and the therapeutic effect. Despite the widespread use of antidepressants in the context of Major Depressive Disorder (MDD), there are no reliable biomarkers of treatment response phenotypes, and a significant proportion of patients display treatment resistant depression (TRD). Fas/FasL system is one of the major pathways in apoptosis and is important to regulate cell proliferation and tumor cell growth. Recently, this pathway has been described to be involved in neurogenesis and neuroplasticity. Functional polymorphisms in the promoter region of FAS and FASL genes have been identified and are known to alter the transcriptional activity of these genes.

We aim to evaluate the role of FAS -670A>G and FASL -844T>C functional polymorphisms in antidepressant treatment response phenotypes, since they have never been addressed in the context of depression and antidepressant therapy.

We genotyped FAS -670A>G and FASL -844T>C functional polymorphisms in a subset of 80 MDD patients followed at Hospital Magalhães Lemos within a period of 18 months.

We found that patients carrying FAS -670 G allele are more prone to have poor prognosis (relapse or TRD: OR=6.200; 95%CI: [1.875-20.499]; p=0.001). We also observed that patients carrying this allele have a higher risk to develop TRD (OR=10.895; 95%CI: [1.362-87.135]; p=0.007). Moreover, multivariate analysis adjusted to potentials confounders showed that patients carrying G allele have higher risk to early relapse (HR=3.827; 95%CI: [1.072-13.659]; p=0.039). No association was found between FASL-844T>C genetic polymorphism and any treatment phenotypes.

To the best of our knowledge this is the first study to evaluate the role of FAS functional polymorphism in the outcome of antidepressant therapy. FAS -670