

Meeting Report

2nd annual meeting of the International Society of Pharmacogenomics (ISP)-

Joint meeting with the Pacific Rim association for Clinical Pharmacogenetics (PRACPG).

Los Angeles, USA, November 3-4, 2003.

This meeting was held in Los Angeles on November 3 and 4, 2003. The historic Millenium Biltmore Hotel was the venue for presentations on the pharmacogenomics of drugs used commonly in clinical practice, latest results of gene mapping from deCode genetics, progress on the HapMap and discussion about the progress of the search for newer drug targets using genomic means. There was a combination of review presentations and research presentation in specific areas. For brevity purposes only the first author only, is quoted in the following meeting description.

Magnus Ingelman-Sundberg, (Sweden), opened the conference with a keynote address, which **summarised existing knowledge in pharmacogenetics**. He covered the correlation between genetic polymorphisms in specific genes of certain drug metabolizing enzymes and the ability to metabolize the drug rapidly or not. Specifically some people metabolize drugs very slowly and are called poor metabolizers. Those with normal rapid processing of the drug are called extensive metabolizers with intermediate metabolizers having less efficient rate of metabolism and ultrarapid having very rapid. For some genes, such as *CYP2D6* these categorisations can be predicted by the number of active metabolizing genes an individual has. On the other hand *CYP3A4* has very few functional polymorphisms in the gene that affect function of the gene despite the fact that the protein made by this gene is involved in the metabolism of about 70% of drugs currently used. *Recently it has been found that that CYP3A4 is differentially spliced to produce a hybrid protein of CYP3A4 and CYP3A43*. One needs to study RNA to study this. He contrasted the knowledge of the pharmacogenetics of drug metabolising genes with the paucity of knowledge relating to the pharmacogenetics of drug transporters and drug receptors. He also suggested there is a great need for prospective clinical studies relating to drug doses and drug choice based on predictive genotyping.

U. Meyer, (Switzerland), discussed the **lessons from 50 years of pharmacogenomics**. He discussed the variability of the human genome with 100 new mutations per individual and that every 3rd gene has frequent polymorphic variants. With the polymorphisms know to affect drug metabolism there is too little known about the dose-effect relationship. Hopefully the future will bring more studies on, therapeutic benefit of genotyping, cost effectiveness of pharmacogenetics, gene test guided therapy and the interaction between drug metabolizing enzymes, drug transporters and environmental effect on drug action.

There were 2 presentations on the use of pharmacogenomics for development of new drugs. The first was by O. Grenet, (Novartis, Switzerland), outlined the **strategies used to develop new drugs**. Currently there are about 500 targets known, but the new methods would aim to expand this to greater than 10000 targets. Expression Chips and other high throughput methods are expected to realise the latter goal. T. Bartfai (USA) described the **ethical, societal and technical aspects in drug development**. He discussed the changes required at the legislative level, drug company level and regulatory agency level to cope with changes found by large scale genotyping. He pointed out that the pharmaceutical industry was in a "split mind" about pharmacogenomics, because it recognises the potential to develop and

tailor drugs to patients, but the latter will result in less numbers of people taking the drugs. The number of new targets developed so far has not met the expectations and the number of new drugs developed is very few.

There was a summary of the **latest results from deCode genetics** from [H. Hákonarson](#), (Iceland). He discussed work on common diseases from the specialized database established in Iceland, which was isolated for 11 centuries. He discussed the work on schizophrenia, stroke and osteoporosis. [D. Goldstein](#), (UK) discussed the **concept of candidate genes in pharmacogenetics**, using studies on pharmacoresistance to anticonvulsant drugs. Studies of MDR1 showed that haplotype analysis was important. The role of other transporter genes, such as MRP1, MRP2 and MDR3 was being investigated. [Francis Collins](#) talked about the International **Haplotype map consortium**. There appear to be blocks of neighbouring SNPs that are inherited as a block (Linkage disequilibrium). Thus the number of SNPs to be studied to scan the genome can be reduced if such a "Hap Map" could be produced. The goal is to develop the Hap Map in 80-90% of the genome. As well as this different ethnic populations need to be sampled.

The first symposium dealt with advances in pharmacogenomics of phase II and phase I drug metabolising enzymes. [Richard Weinshilboum](#) (USA) presented advances in phase II drug metabolising enzymes, discussing the **genetics of Thiopurine S Methyl-Transferase** and describing how the protein level influenced clinical outcome. He discussed the pharmacogenetics of methyl and sulphate conjugation with a detailed discussion of SUL1A3. [J. Azuma](#) (Japan) followed him who discussed the clinical **relevance of the Nat-2 polymorphism** related to hepatotoxicity in the treatment of tuberculosis. He presented several prospective studies. Nat-2 slow acetylators had doubling of the liver enzyme, ALT, in 100% of subjects compared with two percent of the slow acetylator group. Plasma concentrations of isoniazid and its toxic metabolite, hydrazine, were also much higher in the slow acetylator group. Population pharmacokinetic modelling allowed a calculation of optimum Isoniazid dosage for each category of acetylators with slow acetylators being recommended one fifth of the dosage of rapid acetylators. [T. Kamataki](#) (Japan) moved to phase I metabolism with description of a case-control study examining the relationship between deletion of the **CYP2A6 gene and lung cancer**. The odds ratios for those subjects who were smokers with the homozygous deleted genotype was 0.41 and it was 0.19 in males. However for male non-smokers it was 1.48.

Symposium 2 related to pharmacogenomics and clinical Medicine. [D. Nebert](#) (USA), discussed some of the **limitations of defining genotype of drug metabolizing enzymes** such as variable expression, phenocopies and the number of different genetic variants such as G-protein receptors. He also pointed out that ethnic differences are complicating interpretation of some of the new information, such as haplotype blocks. [J. Kirchheiner](#) (Germany) showed the difference in **drug dosage** required when **CYP2D6** genotype is known. [A. Somogyi](#) (Australia) discussed the **opioid receptors, CYP2D6 and MDR1, and efflux pump transporter**.

Symposium 3 continued with discussions on cancer and cardiovascular risk. [J. Weinstein](#) (USA), discussed the **bioinformatic approach to cancer drug discovery** as well as the study of 60 cancer cell lines used to screen >100,000 compounds since 1990. He emphasised the new technology generates vast amount of data. The National Cancer Institute has developed new electronic search strategies, which speed up searches by a factor of ten. [D. Flockhart](#) (USA), talked about the **discovery of a new compound for breast cancer treatment** (Edoxifen) where CYP 2D6 and CYP2C9 seem to be important in metabolism. [R. Krauss](#) (USA), presented

information about the [Pharmacogenetics and Risk of Cardiovascular disease](#) project (PARC), which is searching for SNPs (individual and haplotypes), in 27 candidate genes for pathways affecting lipoprotein and drug metabolism).

Symposium 4 dealt with the application of pharmacogenomics to psychiatry. It started with [N. Ozaki](#) (Japan), who presented **candidate gene studies for the drug risperidone**, used in psychiatry. Haplotypes were investigated in 73 patients and clinical response to therapy was evaluated. A DRD2 haplotype tended to correlate with better clinical performance with a 40% improvement. **Tardive dyskinesia** was discussed by [Bernard Lerer](#) (Israel). 635 patients from 5 countries were studied and an association of symptoms and HTR2A genotype was found. This association only appeared to be significant in older patients. [G. Turecki](#) (Canada) discussed the **pharmacogenetics of bipolar disorder** and also studies on lamotrigine and panic disorder. [A. Serretti](#) (Italy), reviewed the **pharmacogenetics of antidepressants** efficacy. This included variants of the Circadian Locomotor Output Cycle kaput (Clock) gene, which showed a possible association with insomnia. Lastly [J. Licinio](#) (USA) discussed studies of **St John's wort and imipramine on hypothalamic gene expression** in the rat. The used Affymetrix expression chips and found 6 common transcripts after both drugs were used. These lead to the identification of human SNPs in genes that were likely to be regulated by one, or other of these antidepressant drugs. The human studies planned are on Mexican Americans; a group rare studied in the past in pharmacogenetic studies.

This was a very full 2 days that brought together an international group with a common interest in pharmacogenomics. Some committees were formed and discussions held about strengthening the International Society of Pharmacogenomics. Hopefully some new collaborations were born and there is eager anticipation to the next meeting in Santorini in October 2004.

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