

Meeting Report of the

3rd annual meeting of the International Society of Pharmacogenomics (ISP)-

Joint meeting with the International Union of Nutritional Sciences (IUNS) task force on genetics and nutrition.

Santorini, Greece, September 30-October 4, 2004.

The third annual meeting of the International Society of Pharmacogenomics (ISP) was held on the island of Santorini (Greece) as part of the second Biologie and Prospective Santorini conference. This conference was entitled From Human Genetic Variations to Prediction of Risks and Responses to Drugs and to the Environment. The meeting was organised by Biologie Prospective, headed by Gerard Siest and the staff of the INSERM Unit 525-Nancy group with the collaboration and support of the ISP and participation of the International Union of Nutritional Sciences (IUNS) task force on genetics and nutrition. The conference was also under the auspices of the French and Greek national societies, European federations and international organisations of laboratory medicine, atherosclerosis and pharmacogenomics. There was an international scientific committee and an international organising committee. The aim of the meeting was to bring together clinicians, laboratory medical scientists and scientists from academic and industrial sources to discuss how human genome variation could be used in understanding drug and nutritional effects on the human body.

Inspiring the minds of the attending scientists was the spectacular view from the Nomikos Conference Centre of the deep blue waters of the Aegean Sea, the distant Islands and the rocky Volcanic outcrop in the Caldera. With the heat of summer bouncing off the stunning white cliff-top buildings, knowledge was bounced from one expert to another enhancing the knowledge of all whom attended.

The outline of the meeting were initial overview (opening) lectures, 3 sessions on cardiovascular diseases, predisposition and polymorphisms), two sessions on nutrigenomics (ecogenomics), two on cancer pharmacogenomics, one on gene regulation, drug targets and biomarkers, one on drug metabolism and pharmacogenomics, one on pharmacogenomics of neurological and psychiatric disorders and the final session on proteomics.

[D.C.Wallace](#), (USA), who spoke about the **mitochondria in health and disease**, started the opening lectures. The mitochondria provide the energy source of the body through the respiratory chain complexes and the processing of carbohydrates and fats. The mitochondria are dynamic and if enough mitochondria cease to function the cell dies. They have been associated with over 50 degenerative diseases and are controlled by 37 mitochondrial DNA genes and over 1000 nuclear genes. The diseases that may be caused by mutations in these genes range from Alzheimers and Parkinsonism to deafness and diabetes. The relationship between mitochondria and prostrate disease is being further investigated.

[S. Antonorakis](#), (Switzerland), spoke about **conserved non-coding regions** that occur throughout the human genome. The function of these regions is not yet known but the high conservation between species suggests that they have important functions. An example was given by the Hx gene which causes pre-axial polydactyly which has an intron which is very near the neighbouring, extremely important Sonic Hedgehog gene. [M. Phillips](#), (Canada), who talked to us about the **International Hapmap** followed this talk. This collaborative effort is attempting to map Single Nucleotide Polymorphisms (SNPs) that represent a block of linkage disequilibrium

aimed to reduce the SNPs required to cover the genome for a whole genome association scan or even to cover a specific area on a particular chromosome. There are 4 populations being mapped to cover different ethnic groups. Details are available at <http://www.hapmap.org/>.

[D. Nebert](#), (USA), then completed the opening lectures with a review of pharmacogenomics and a critical look at **progress to “individualised drug therapy”**. He pointed out that often a too simplistic approach was taken to try and understand the genetic influence on individual drug effect. There are many steps in drug action (absorption, transport, metabolism, receptor effects and excretion) and hundreds of potential genes involved. The genome is dynamic with new mutations, differential splicing, up and down regulated genes, gene copies, conserved non-coding regions, one mutation causing multiple phenotypes and one phenotype being caused by multiple mutations, including mutations in different genes. There is still much work to do on the Human genome project. New sciences such as transcriptomics, metabolomics and proteomics may go some way to do this but the complexity means that exact prediction of drug response for many drugs is still a long way off. The practicing physician is not expected to use genetic tests for prediction of drug response for 5-10 years.

The first session on Cardiovascular disease, started with a presentation by [C.C. Liew](#), (USA), who outlined the **use of expression arrays in studying cardiovascular disease**. Such as dilated cardiomyopathy and hypertrophic cardiomyopathy. [S. Viskis Siest](#), (France), outlined the **Stanislas Cohort study**. Originally there were over 1000 nuclear families but 190 families have been selected to specifically study lipids, blood pressure and adhesive and inflammatory molecules. Major genes were examined for their individual contribution to the genetic variance and their contribution to lipid levels. [R. Fricke-Schmidt](#), (Denmark), talked about the Copenhagen city heart study, which screened the highest and the lowest individuals with HDL **cholesterol levels, and looked at SNPs in the ABCA1 and ZNF202 genes**. They found 6 SNP genotypes and studied haplotypes. genotype/phenotype studies were then made and mutations in these 2 genes were shown to contribute to HDL cholesterol levels. The session concluded with [J. Leger](#), (France), who has **developed an array** which has 5000 muscle, (skeletal and cardiac), specific genes. These chips were used to study end stage heart failure and chronic atrial fibrillation. Genes that were up and down regulated were targeted and principle component analysis was used to study clusters.

The second session on cardiovascular diseases started with [M.H. Hofker](#), (The Netherlands), who described the **use of transgenic animals in studying polymorphisms related to cardiovascular diseases**. An APOE knockout mouse has been developed which is highly susceptible to atherosclerosis. Expression arrays were used to study genes involved and inflammatory pathway and lipid genes were found. Also mouse crosses have been made to detect novel genetic loci. A different study was briefly presented that found that a substance in coffee, (cafeosterol), raises cholesterol and is filtered out in filter coffee. [V. Mooser](#), (USA), talked about studies of **metabolic syndrome** in the multinational GEMS project. This project consists of 1500 cases and 1400 controls. Linkage was performed and at least one promising locus has been found. [I. Wybanska](#), (Poland), also discussed the **metabolic syndrome** and looked at 14 specific genes. Finally [G. Dedoussis](#), (Greece), discussed **familial hypercholesterolemia (FH)** in Europe. The LDL receptor was studied by reviewing the published European LDLR mutation data.

The conference organiser, [G. Siest](#), (France), started the final cardiovascular session. He presented a review of the **pharmacogenomics of cardiovascular**

disease. He outlined a five-step approach to study incorporating environmental effects. **R.M. Kraus**, (USA), presented work from the **PharmKB network**. Tagging SNPs were studied in LDLR, APOAV and CETP and specific SNPs were found to predict increased response, of a specific LDL to a low fat diet. **B. Winkelman**, (Germany), discussed the **complexity of cardiovascular studies** such as the confounding effect of age in classifying subjects as “responders” or “non responders”. **A. Carrié**, (France), discussed the **response to statins in hypercholesterolemia** looking at some of the key genes in lipid metabolism. A common OATP-C polymorphism is functionally implicated in the inter-individual variation in response to fluvastatin. **A. Syvänen**, (Sweden), described **micro-array genotyping sequencing** for testing 74 SNPs in 25 genes involved in blood pressure regulation. The individuals studied were involved in the Silvhia trial, which used ibersatin and atenolol. The preliminary results identified 4-5 SNPs that explained 50% of the variance, 2 specific SNPs in the angiotensin gene that were associated with reduction in blood pressure for patients on atenolol and a SNP in the apolipoprotein B gene that was associated with reduction in blood pressure for the drug, irbestatin. Finally, **P. Charron**, (France), emphasised the need for adequate sample size and the demonstration of repeatability of results in a separate sample before accepting pharmacogenomics results. He described the **Eurogene heart failure study** involving 10 European centres using 2676 subjects.

The first section on nutrigenomics, (ecogenomics) started with work from **J. Ordovas**, (Boston), who talked about **Lipid metabolism** and the Framingham heart study. Some of the findings have been reproduced by studies in populations from Singapore. **R. Jirtle**, (USA), presented information on **imprinted Genes and transposons**. He discussed work in mice that showed that early post-natal dietary methyl deficiency affected the imprinting of Igf2. Maternal dietary methyl donor supplementation during pregnancy alters offspring coat color and this reduces the offsprings susceptibility to obesity, diabetes and cancer. **A. Simopoleos**, (Greece), outlined the importance of the **omega 6/omega-3 ratio essential fatty acid ration** in determining cholesterol levels and heart disease risks. **J. Whitfield** (Australia) discussed **alcohol and gene interactions** with particular reference on alcohol dependence. **H. Hubacek**, (Czech Republic), discussed the relationship between a **polymorphism in 7 α -hydroxylase and cholesterol** responsiveness to dietary changes. Finally **C. Bonati-Pellié**, (France), presented a model for predicting **gene and environment effects**.

The second section on nutrigenomics had 2 presentations. The first was on **celiac disease**, (**C. Wijmenga**, The Netherlands) and the second on **FABP2 gene polymorphism and insulin** resistance (**E. Delvin**, Canada). As on the first day the final session was followed with brief presentations of several posters. That evening there was a Round Table discussion of “education for pharmacogenomics needs for clinicians, health specialists and patients. A summary of this is published on the conference website, (<http://pagesperso.laposte.net/pharmacogenomic/upload/index.php>), and its contents are going to be developed into a policy statement for the International Pharmacogenomics Society.

The third Day of the conference saw the 2 sessions on cancer pharmacogenomics. **S. Hanash**, (USA), set the scene by describing, the different **techniques of investigation in the post genome era**. **M. Makrigiororgus**, (USA), described the technique of **inverse PCR-based amplified restriction fragment length polymorphism** to measure the degree of low level mutations. Seven of 10 sporadic colon tumours showed widespread low-level mutations. **E. Taioli**, (Italy), talked about **xenobiotic metabolising enzymes and cancer risk**. He described the GSEC study

of 54,000 subjects. The **CYP2A6 polymorphism and Tobacco** related cancer was presented by [T. Kamakati](#) (Japan), a deletion of the whole gene was found in Japan, and was found to be associated with lower risk of cancer. A case-control study showed that CYP2A6*4C is associated with reduced cancer risk. [D.Chan](#), (USA), described proteomic and **bioinformatic** approaches to pharmacogenomic study.

The second cancer pharmacogenomics section started with [S. Lilleberg](#), (USA), with a summary of developments in **oncogenetics**. This was followed by [P. Righetti](#), (Italy), described a **proteomic approach to drug resistance** in cancer cells. [O. Mikhaililova](#), (Russia), described a case-control study in the Novosibirsk region and the **frequency of SNPs in CYP1A1 and CYP1A2** was documented. Certain alleles were higher in hormone dependent cancer patients. **Thymidilate synthase polymorphisms** were studied and correlated to response to 5-fluorouracil therapy by [J. Boyer](#) (France). [V. Ribeiro Marques](#), (Portugal), looked at SNPs in **CYP3A4** and its transcriptional nuclear regulator PXR. Known polymorphisms were studied in a case-control study but were not found in the population sample. Thus these variants don't appear to be related in the breast cancer etiology. Finally **N-Acetylcysteine**, which increases glutathione, was shown to enhance MRP1 –mediated doxorubicin resistance by [I. Akan](#) (Turkey).

Specific genes, regulation and drug targets were the name of the next session. [V Shankey](#), (USA), presented the use of **flow cytometry** in pharmacogenomics and discussed the effect of Gleevec. [A. Dembinska-Kiec](#), (Poland), described studies of umbilical cord progenitor **stem cells** during angiogenesis and [R. Caffey](#), (USA), used seldi protein chip technology to study **Chagas disease** using a panel of markers. [B. Feiden](#), (France), looked for **novel bacterial RNAs** by transcriptome analyses and Northern blots. [L. Sheffield](#), (Australia), presented a pharmacogenetics study of **acetaminophen use in children** and showed that CYP1A2*1F was associated with occult liver damage. [M. Brito](#), (Portugal), studied the presence of the ϵ 4 allele of **APO E** in young adults with hypercholesterolemia and the frequency was significantly higher than the Portuguese population.

Drug metabolism (DM) was the topic of the next session covering different families of genes involved in DM. [P. Beaune](#), (France) gave an **overview on CYP** polymorphisms in DM. [J. Kirchheiner](#), (Germany), gave a summary of CYP2D6 polymorphisms and their effect on **drug dosage** and metabolizer status. [V. Vasiliou](#) summarized **aldehyde dehydrogenase** polymorphisms and [G. Scmitz](#), (Germany), discussed the **ABC transporter polymorphisms**. [J. Vonderscher](#), (USA), described how pharmacogenomics was being used at all stages of new **drug development**.

The session on neurological and psychiatric disorders had presentations on depression, pain management, schizophrenia and prolonged QT interval. [J. Licinio](#), (USA), described the randomised-controlled trial on **Mexican Americans** given fluoxetine for depression or placebo. 195 patients were randomised with a 20-50% response. Specific candidate genes were looked at the results are awaited. [C. Flordellis](#), (Greece), discussed the **adrenergic receptors** and [S. Wong](#), (USA), discussed **forensic pharmacogenomics** as well as the pharmacogenomics of pain management. [E. Ntzani](#), (Greece), reviewed the many and often conflicting studies in association studies in schizophrenia. [A. LLerena](#), (Spain), talked about CYP2D6 and CYP2C9 changes and **QTc interval lengthening** in treatment with psychotropic drugs. There was a relationship between lengthening of the QTc interval and the debrisoquine metabolic ratio. [S. Yim](#), (Korea), described association studies on more than 100 candidate genes for susceptibility to **schizophrenia**. Several associations were confirmed.

The final session was entitled From “Genomics to Proteomics”. [J. Hoheisel](#), (Germany), talked about the development of **DNA-,protein and peptide microarrays**. These are being developed to be used in molecular epidemiology, cancer diagnosis and treatment including early diagnosis from bodily fluids. [H. Langen](#), (Switzerland), talked about the development of “**disease specific proteins**”. The method involves initial separation with gel electrophoresis and then mass spectrometry for rapid identification of the proteins. [W. Arap](#), (USA), explained the technique of isolating **small peptides** from bacteriophage. His work was aimed at the peptides involved in angiogenesis. Finally [M. Naraghi](#), (Germany) talked about how **medical care** may be integrated, in the future, with a combination of imaging, molecular methods and IT.

Each day of the conference there were poster sessions, with some selected for brief presentation at the end of the day. There were some seminars from commercial participants and the Gala dinner was held at a Santorini winery. A pottery viewing and a gallery viewing of a local artist preceded this. The conference photograph was taken on the front side of the Nomikos conference centre with the spectacular caldera as the background. All of this added up to a truly beautiful and notable conference on Santorini.

The abstracts of the conference are published in *Clin Chem Lab Med*,2004 ;**42**: A21-A60.

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