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Abstracts*)

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EUROPEAN SOCIETY OF PHARMACOGENOMICS AND THERANOSTICS: GOALS AND DRUG SAFETY

Gérard Siest
Research Team "Cardiovascular Genetics", Nancy University, 30 rue Lionnois, 54000 Nancy, France
Email: Gerard.Siest@pharma.uhp-nancy.fr

The European Society of Pharmacogenomics and Theranostics (ESPT) is a non-profit organization. Its aims are to promote education and reaction in pharmacogenomics and theranostics, to ensure high standards in their application to clinical practice and to facilitate contacts between all persons who share these aims, particularly those working in Europe. The Society will encourage and seek to integrate basic multidisciplinary research approaches and their translation into clinical benefits, and professional and public education in all areas of human pharmacogenetics, clinical pharmacology and laboratory medicine. But more specifically, goals are:

- To facilitate the prototyping, introduction and use of pharmacogenomics data in the clinic
- To increase multidisciplinary collaborations between participating disciplines including, but not limited to, pharmacologists, clinical chemists, laboratory medicine specialists, geneticists and clinicians
- To encourage and participate in independent clinical trials and in collaboration with the pharmaceutical industry
- To develop and propose guidelines and recommendations working together with the appropriate agencies
- To propose teaching programmes and courses
- To lobby for European grants and support mechanisms
- To establish an Outreach Programme for teaching and clinical trials to territories beyond the EU, building on established networks in Latin America, Africa and China

For the patients, outside to better adapt the drug dosage in function of the polymorphisms, pharmacogenomics will help to reduce adverse drug reaction (ADR) (1).
To starting with the information described in Lazarou, Pomeranz and Cory paper on ADR in hospitalized patients in the USA (6.7% serious effect and 106000 fatal on 22116000 hospitality patients), it is necessary to describe the drug metabolizing enzymes genes involved and the main drugs which could create problems.
Avoidable and non-avoidable ADRs should be defined through different types of mechanistic schemes. Research will also be necessary for validating the pathways involved. Patient and clinicians information are important tools to be developed through databank and direct access recommendations and guidelines on the website. This also could be a task of the new ESPT.

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PHARMACOGENOMICS: PAVING THE PATH TO PERSONALIZED MEDICINE

George P. Patrinos, Marianthi Georgitsi
University of Patras, School of Health Sciences, Department of Pharmacy, University Campus, Rion, GR-26504, Patras, Greece
Email: gpatrinos@upatras.gr

Each revolutionary change in human medicine, from antibiotics to vaccines, has moved the practice of healthcare toward improved patient treatment. Pharmacogenomics promises to usher in an era of individualized patient care or personalized medicine. Pharmacogenomics uses markers in individuals' genetic code to better identify an individual's response to a certain drug, towards achieving individualized (personalized) therapy. This has been made possible not only from the deciphering of the Human Genome DNA sequence, but also from major technical and scientific advances of the last decade in the field of genetic testing. In patient care, Pharmacogenomics help to identify patients for whom a certain drug will have no or marginal benefit and will serve to reduce wastage drug, since the vast majority of drugs only work in 30–50% of the people on whom they are used. Also, pharmacogenomics can detect disease at an earlier stage, when it is easier to treat effectively, enable the selection of optimal therapy, reduce adverse drug reactions, and increase patient compliance with therapy. Pharmacogenomics can also assist pharmaceutical companies to achieve more predictable clinical trial outcomes, to improve the selection of targets for drug discovery, to reduce the time, cost and failure rate of clinical trials, to revive drugs that failed clinical trials or were withdrawn from the market and to avoid withdrawal of marketed drugs. In general, pharmacogenomics shift the emphasis in medicine from reaction to prevention and hence contribute to reduce the overall cost of healthcare. Despite its promise, pharmacogenomics faces significant ethical, technical and societal challenges, which need to be addressed to enable pharmacogenomics to reshape the pharmaceutical industry.

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CHALLENGES AND OPPORUNITIES FOR SYSTEMS BIOLOGY IN 21ST CENTURY HEALTHCARE

Adriano Henney
Obsidian Biomedical Consulting Ltd., Macclesfield, Cheshire, SK10 2UN UK
Email: adriano.henney@obsidian-biomed.com

In the next 20 years we will have to face the challenges of healthcare provision to an increasingly ageing population, where chronic, complex, mutifactorial diseases will be common. At the same time, the successful delivery to the market of innovative medicines to treat these diseases is limited, with ever increasing costs and lengthy development times. This despite the wealth of information gathered post-genome, and the expectations that it would improve our understanding of disease and increase our ability to target therapies more effectively.
Whilst we have learned a lot, we have become increasingly reductionist in our approaches, and have consequently lost the physiological context in which complex diseases operate. Systems approaches combining theoretical and experimental techniques to simulate complex networks offer a potential way to tackle these challenges. This talk will offer personal perspective on this and introduce the work being done in the German Virtual Liver Network, a major national investment in Systems Biology targeting the understanding of the physiology of this critical organ in heath and disease.

TRANSLATING PHARMACOGENETICS INTO CLIICAL PSYCHIATRY AND ITS CLINICAL IMPLICATION FOR WORLD POPULATIONS

Adrián LLerena, Eva M. Peñas-LLedó, Pedro Dorado
Clinical Research Centre (CICAB), Extremadura University Hospital and Medical School, 06080 Badajoz, Spain (www.cicab.es)
Email: allerena@unex.es

Translation of pharmacogenetics into clinical psychiatry practice holds a great promise. However, there appear to be many limitations for its current use. One of the problems is that most of available data have been extrapolated from healthy volunteer studies, and therefore evidence during routine clinical treatment under steady state conditions is scarce. On the other hand, most of the drugs used for the treatment of mental disorders have active metabolites, or enantiomers with different pharmacological activity and metabolism and more than one enzyme might be also relevant for its elimination. Thus, clinical evaluation requires to considerate the variability due to pro-drugs and active metabolites at the same time. Moreover, in many cases the dose-concentration or concentration-effect relationships are not well defined, which makes meaningless to predict them by pharmacogenetic analyses. In clinical psychiatry drug polytherapy is common making the prediction of response quite complex. An additional problem is that sometimes enzyme activity is assumed from genotype. However the prediction of adverse reactions is better defined and accurate, therefore current pharmacogenetic knowledge should be used for "active" pharmacovigilance programmes.
The use of prospective testing of all psychiatric patients must be considered. Nevertheless, it could be cost-effective for specific cases for which there is reasonable scientific evidence (i.e. about the detection of CYP2D6 PMs and UMs during treatment with typical antipsychotics, tryciclic and SSRI antidepressants). Moreover recently the relationship with suicide has been remonstrated, which might be related to previous studies about the role of CYP2D6 pharmacogenetics on endogenous metabolism and its implication for psychological functioning and psychopathology. We have also found data about the implication of CYP2D6 genetic polymorphism for suicide among eating disordered patients. This new data linked pharmacogenetics to theranostics.
Data will be discussed in the phrame of interethnical variability of drug response and its relevance for psychiatry. The interethnical variability on genetic polymorphism may be related to the population variability obeserved in the response of psychotropic drugs. With the purpose of fulfilling this information gap and to promote collaborative pharmacogenetic/genomic research in Latin America and the Iberian peninsula, a network – the Iberian American Network of Pharmacogenetics and Pharmacogenomics-was created in 2006 (www.ribef.com). This initiative represents a promising step towards the inclusion of Latin American populations among those who will benefit from the implementation of pharmacogenetic principles and tools in drug therapy. The influence of environmental as well as endogenous factors might have influence in each location, thus clinical trials might be necessary in several populations in order to recommend the right dose to each individual in each country.

PHARMACOGENOMICS OF ANTICOLAGUANT AND ANTIPLATELET AGENTS: READY FOR CLINICAL PRACTICE?

Vangelis G. Manolopoulos
Laboratory of Pharmacology and Clinical Pharmacology, Democritus University of Thrace Medical School, Dragana Campus, Alexandroupolis, Greece
Email: emanolop@med.duth.gr

Coumarin derivatives such as warfarin, acenocoumarol and phenprocoumon constitute the world-wide oral anticoagulant treatment of thromboembolic disorders, while clopidogrel is the most commonly prescribed antiplatelet treatment. Response to therapy to these drugs exhibits significant variation among patients. A great proportion of this variation is due to genetic background of individuals.
In the case of coumarin derivatives, variations both in the genes of cytochrome P450 enzyme *CYP2C9* and vitamin K reductase *VKORC1* influence individual responses to anticoagulant therapy. *CYP2C9*2* and **3* variant alleles result in decreased CYP2C9 enzymatic activity affecting coumarin pharmacokinetics, while *VKORC1 -1639G>A* polymorphism influence pharmacodynamics response to coumarins. It appears that lower doses of coumarins may be best for patients with variations in one or both of these genes and efforts are made to incorporate this knowledge in currently used dosing regiments. Towards this direction, pharmacogenetic-based dosing algorithms are currently tested in large prospective, randomized, pharmacogenetic clinical trials both in Eurpoe and the USA. It is hoped that the results of these trials will provide the solid basis for broadly implementing genotype-guided dosing of anticoagulant therapy in the clinical routine.
The antiplatelet agent clopidogrel is a pro-drug which is converted to an active metabolite by the polymorphic enzyme CYP2C19. Several studies in the last 5 years have shown that carriers of variant *CYP2C19* alleles (*CYP2C19*2* and **3* loss of function alleles) have impaired ability to metabolize clopidogrel to its active metabolite and as a result decreased inhibition of platelet aggregation and increased cardiovascular risk. Additionally, a novel allele named *CYP2C19*17* has been associated with increased enzyme transcription and better response to clopidogrel. Carriers of this allele may exhibit improved prevention of thrombotic events, but may also have increased risk of bleeding events. Efforts are made to implement *CYP2C19* genotyping in the clinic prior to clopidogrel prescription.
It is anticipated that broad implementation of pharmacogenomics in routine cardiology clinical practice will help ameliorate risk of bleeding or thrombotic events and increase effectiveness of both anticoagulant and antiplatelet agents.

DRUG TRANSPOTERS AND IMATINIB PHARMACOGENOMICS

Janja Marc, Albin Kristl
University of Ljubljana, Faculty of pharmacy, Ljubljana, Slovenia
Email: Janja.Marc@ffa.uni-lj.si

Chronic myeloid leukaemia (CML) is a mieloproliferative malignant disease of hematopoietic stem cell and it is present in 15-20% of adult patients with leukaemia. The natural course of the disease lasts 3 – 5 years and has three phases: chronic, in which 85% of patients are diagnosed, followed by an accelerated period, leading to final blast transformation. Since 2001, the molecular therapy of CML began with imatinib, the first tyrosine kinase inhibitor (TKI) eight-year survival of patients with CML is as high as 93%. Despite the high average bioavailability, the interindividual variability in pharmacokinetic parameters of imatinib is significant: 36% for the clearance and 63% for the volume of distribution – both resulting in a large variability of imatinib plasma concentrations (1). It is known that imatinib is a substrate of OCT1 (Organic Cation Transporter 1), which transports it into target cells. Patients whose OCT1 activity was high, responded well to imatinib treatment in a much larger percentage compared with the patients with low OCT1 activity regardless of dose. Among the reasons for differences in the activity of OCT1, the expression and polymorphisms of SLC22A1 gene (a gene coding for OCT1) are

important, since nearly 10% of the population has almost negligible activity of these transporters In addition to OCT1, imatinib is also a substrate of transporters ABCB1 (P-gp or MDR1) and ABCG2 (BCRP), which shown the influence on the drug elimination from the organism and from the cancerous target cells and can develop drug resistance. Several mechanisms of resistance exist and it seems that the resistance is either directly or indirectly (through increased emergence of TKI resistant clones) linked to insufficient drug concentration at the site of action. To date, over 50 types of mutations that cause both primary and secondary resistance and result in different responsiveness to imatinib are described. While the cause of mutations is not yet definitively explained it is very likely that the activity of Bcr-Abl tyrosine kinase itself leads to instability in the genome of malignant hematopoietic stem cells. Therefore, some researchers view the low drug concentration at the site of action and consequently insufficient inhibition of Bcr-Abl, as a possible cause for the development of mutated clones and subsequent selection of TKI resistant ones (2). Currently, no test in clinical use can predict which patients will develop a resistance in the future. Several genome-wide studies as well as studies of genes for the transporters, were made to find markers which would correlate to the response to the treatment with imatinib. The polymorphisms of the genes for transporters and metabolic enzymes and different expression of these genes, particularly in target cells could be the reasons for interindividual variability of intracellular imatinib concentrations and its metabolites.

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