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Commentary

Workshop outcomes report: Initiatives to establish a European Network of pharmacogenetics/genomics and progress☆

Anke Hilse Maitland-van der Zee[a,*], *Katherine Aitchison*[b], *Julia Kirchheiner*[c],

For the European Pharmacogenetics/Genomics Sciences Community

[a] *Division of Pharmacoepidemiology and Pharmacotherapy, Faculty of Science, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands*

[b] *Clinical Neuropharmacology, MRC SGDP Centre, and Division of Psychological Medicine and Psychiatry, Institute of Psychiatry, London, UK*

[c] *Department of Pharmacology of Natural Products and Clinical Pharmacology, University of Ulm, Germany*

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1. Background and aims

This report is a distillation of a workshop entitled: 'Workshop on Pharmacogenetics/Pharmacogenomics, Including Relevance for Personalised Medicines' held in November 2006 in Utrecht, The Netherlands. The aim was to bring European scientists working in the field of pharmacogenetics together in order to develop a European roadmap for improving collaboration and research on pharmacogenetics in Europe. It was organised by EUFEPS and co-sponsored by the Utrecht University and by the FIP Board of Pharmaceutical Sciences. The newly formed Dutch Top Institute Pharma provided financial sponsorship.

Pharmacogenetics and pharmacogenomics are emerging disciplines that focus on genetic determinants of drug response at the levels of single genes or the entire human

☆ As represented by the delegates of the Workshop on Pharmacogenetics and Pharmacogenomics on November 13–14, 2006 in Utrecht, The Netherlands.

* *Corresponding author*. Tel.: +31 302534042; fax: +31 302539166.
E-mail address: A.H.Maitland@uu.nl (A.H. Maitland-van der Zee).

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genome, respectively. Although, pharmacogenetics is not a new field (Sadee, 1999), it has recently enjoyed a surge in activity as a result of the availability of better tools and a realisation of potential benefit by both the pharmaceutical industry and governmental regulatory bodies. The applied objectives of pharmacogenetics include improving drug efficacy, avoiding harmful side effects, and improving the efficiency and timeliness of drug response. There are many research-groups in Europe that focus on pharmacogenetics/genomics projects, but there is not yet any European Network, nor strong European financial support in order to facilitate and stimulate collaboration between these different groups in Europe. This workshop provided a forum for group leaders in the field of pharmacogenetics/genomics to discuss the opportunity of forming a European Network.

The aims of this workshop were:

- to exchange state-of-the-art pharmacogenetics/genomics research being conducted in Europe;
- to ascertain where and what is being done in European pharmacogenetics/genomics research (localization of research activities);
- to find out whether there is interest in forming a European Network;
- to evaluate the possibilities for obtaining European funding. What are the chances for multicentre pharmacogenetic/genomic research to be funded in the 7th European Framework Programme for Research and Technological Development?
- to foster future collaborations within Europe. For example, establishing a common database or gene-bank, and a European pharmacogenetics/genomics website (European activities in contrast and in cooperation with the US activities PharmGKB network and database);
- to find out what exists concerning training and education in pharmacogenetics/genomics within Europe.

Parallel and repeated small group discussion sessions were organised into three topic areas: What would be the roles of the pharmacogenetics/genomics network? How to obtain more/better funding for research in Europe? and how to expand and improve collaboration and sharing, e.g. databases in Europe?

Discussion leaders collated summaries of the parallel sessions, and an overall summary of the three topics was presented in a final discussion session.

The objective of this report is to document the contents of the workshop and the final discussion session in order to provide future direction for the European pharmacogenetics/genomics network and potential funding.

2. Never a single gene alone

Kim Brosen (University of Southern Denmark) presented his view on the translation of pharmacogenetics of antidepressants into clinical practice. He said that drug response:

(1) is always to some extent determined by genetic factors;
(2) however, never determined by a single gene alone;
(3) never determined by a group of genes only;
(4) but it is always a result of mutually interacting genes with important modifications from environmental and constitutional factors.

Genotyping before treatment, as a tool in tailoring the right drug to the right patient, will be possible if drug response is mainly determined by a single or just of few genes characterised for all clinically relevant single nucleotide polymorphisms (SNPs). Furthermore, all clinically relevant environmental and constitutional influences should be known and measurable, both when treatment is initiated and during drug treatment. In clinical psychopharmacology, the two most important polymorphic drug metabolic enzymes are cytochrome P450 (CYP) 2C19 and 2D6 (Brosen, 2004). Studying those two cytochrome P450 enzymes has been a hallmark of the last 25 years of pharmacogenetic research, especially in Europe.

3. Statistical power needed

Anke-Hilse Maitland-van der Zee (Utrecht University) described the pharmacoepidemiological approach to pharmacogenetics. Although, pharmacogenetics is not a new field, in general, developments in the laboratory for SNP collection have advanced far greater than advances in data analysis and interpretation, she stated. It is now feasible to genotype thousands – or even hundred thousands – of SNPs, but most studies lack sufficient statistical power to detect gene-drug interactions. Drug response is the result of numerous interactions among various biologic pathways. Therefore, it is appropriate to examine sets of SNPs in different genes, or to do a genome-wide scan, analysing multiple SNPs jointly, rather than testing each SNP in isolation (Maitland-van der Zee and Boerwinkle, 2005). When multiple SNPs are analysed, the sample size and study design become very important. Newer methods, such as random forests and Bayesian Networks, are emerging from the field of computer science and migrating over to the field of pharmacogenetics (Rodin et al., 2005).

4. Drug metabolism and physiological effects of genetic polymorphisms

Julia Kirchheiner (University of Ulm) gave a presentation on the pharmacogenetics of CYP 2C9/Nonsteroidal anti-inflammatory drugs (NSAIDs) and clinical implications (Kirchheiner and Brockmoller, 2005). At least 16 different registered NSAIDs are, currently, known to be at least partially metabolized by CYP 2C9 (among others: acetylsalicylic acid, azapropazone, celecoxib, diclofenac, ibuprofen, indomethacin, lornoxicam, meloxicam and naproxen). Beside NSAIDs, drugs such as vitamin K antagonists, statins, oral hypoglycaemic drugs are metabolized by CYP2C9. However, this enzyme also plays a physiological role in arachidonic acid metabolism and the function of the genetic polymorphisms is currently being studied within the context of cardiovascular disease. The knowledge on genetic polymor-

phisms within drug metabolizing enzymes not only impacts drug therapy but might also affect symptoms and diseases directly.

5. Industry progress and vision

Reinhold Kerb (AstraZeneca R&D, Sweden) gave his industry vision on pharmacogenetics/genomics. Pharmacogenomics has potential to impact on drug discovery and development process at many stages of the pipeline, contributing to target identification and validation; assessment of exposure, efficacy and toxicity of compounds; identification of disease subgroups; and the prediction of responses of individual patients. Almost all pharmaceutical companies have implemented pharmacogenomic approaches into their development process to a certain extent. However, most seem to follow a rather conservative approach of collecting DNA samples from clinical trials. The main driver to apply the pharmacogenetics/genomics 'toolbox' is to meet requests from regulatory authorities. In reality, pharmacogenomics has already been used to demonstrate that molecular data facilitates assessment of disease heterogeneity, and, thus, that molecular markers of response to drugs, such as gefitinib (Iressa) and trastuzumab (Herceptin), can be identified. Knowledge of genetic variation in a drug target ensures that the new chemical compound is active against the most common form of the protein and allows early assessment of the clinical significance of polymorphisms through the appropriate design of preclinical studies and use of relevant animal models. Only a structured, methodological, science-driven process will develop pharmacogenomic/genetics into an efficient tool to take full advantage of these methods.

6. Funding levels and recent findings

Leif Bertilsson (Karolinska University Hospital, Sweden) has been a principle investigator for pharmacogenetic grants in both Europe and the USA. He reported, on the large efforts the NIH spent during the past years in order to strengthen pharmacogenetic/genomic research within the US. The PharmGKB (The Pharmacogenetics and Pharmacogenomics Knowledge Base) was created as part of this NIH-funded programme. This database and network are an impressive and growing resource. In Europe, there is not yet the same level of support for pharmacogenetic/genomics research. At present, the European Commission is funding one project in pharmacogenetics/genomics (GENDEP, Genome-based therapeutic drugs for depression; www.gendep.iop.kcl.ac.uk). Funding for follow-on work from this project and for other pharmacogenetics projects is needed.

Leif Bertilsson also focussed on the large interethnic differences in pharmacogenetic polymorphisms, for example, the large differences in CYP enzyme polymorphisms within different populations and the importance for specific studies on drug therapy in different populations (Mirghani et al., 2006). Current studies include the pharmacogenetics of efavirenz in Ethiopia and Tanzania.

7. European collaboration should improve

Dolores Ibaretta (scientific officer of the European Commission) commented a report from the EU, entitled "Pharmacogenetics and pharmacogenomics: state-of-the-art and potential socio-economic impacts in the EU" (IPTS 2006, EUR 22214 (http://www.jrc.es/home/pages/detail.cfm?prs=1387). Pharmacogenetics was, in fact, recognised as an important field of interest in the European Scientific Community, she stated, including having more publicly research groups than the US and Japan. Nevertheless, the public and private sector of funding is still characterised by a clear USA leadership. In addition, European Networks promoting better collaboration between research groups across Europe are missing. In the USA and Japan, establishment of consortia has formed an important pillar for networking activities and knowledge transfer. The EU could benefit from similar efforts. More incentives to enhance collaboration between academia and industry may also need to be better promoted through appropriate European funding programmes, more coordinated funding being the key issue in this context.

8. Outcomes summary

The recommendations of the final discussion were:

8.1. *Better exploitation of Europe's initial pre-eminence in the subject*

The tradition for studying inter-individual variability in drug response, at the genetic level, was established originally in Europe, where there is longstanding experience in countries such as Sweden, Switzerland, Denmark, Germany, France, The Netherlands and the UK. Nevertheless, the importance of pharmacogenetic research may have been better recognised in other regions, in particular by the USA and Japan, also resulting in substantial initiatives to extend the knowledge base of the subject in various disease areas. Against this background:

(a) USA investigators have been able to be more pro-active in this area of research, leading to high impact publications and patents, as well as translation into clinical practice;
(b) there is a significant flow of both young and senior scientists out of Europe to the USA—which will have a detrimental impact on pharmacogenetic and other fields in Europe.
(c) The global pharmaceutical industry has recognised the increasing role of the USA in this area, and now regards it as the first port of call for undertaking studies and getting advice on pharmacogenetics for their new drugs in development.

In order to improve European research and reverse these trends, as needed, substantial funding into pharmacogenetics seems to be urgently needed. Workshop participants were of the opinion that there is already a strong, albeit dispersed, infrastructure, and, therefore, that relatively little effort would be required to collect information on existing research

activities to support, coordinate and further build a powerful knowledge and research base within Europe.

8.2. *Additional use of information from a European population*

The European population has a unique ethnic and racial mix, which is not identical to other Caucasian populations (even other apparently "Caucasian" populations). There are many differences in allele frequencies of genes in populations in Europe (e.g. the increase in frequency of ultra-rapid drug metabolizers with respect to CYP2D6 from Northern to Southern Europe). However, there are many other genetic characteristics of European populations that we need to define to ensure that they get the best drug therapy in the future.

8.3. *Further mobilising the talent and information within the European pharmaceutical industry*

There is a large European pharmaceutical industry, and there are many SMEs prospering, also having an interested in the area of pharmacogenetics/genomics. No one would question that it is important that Europe has an active, expanding and vibrant (academic) research community in pharmacogenetics to engage with industry and, thereby, maintaining the competitiveness of the European pharmaceutical sector. Recent efforts to increase European strengths and competitiveness include, for example, the Innovative Medicines Initiative (IMI), focussing on efficacy, safety, information management and training and education. There are also the initiatives towards coordinated systems approaches in drug discovery, development and utilisation.

9. Network objectives

The European Network (of excellence in pharmacogenetics/genomics) to be fully established would be the voice of the European science community in pharmacogenetics and pharmacogenomics. Objectives of it would include:

9.1. *To provide a platform for gathering and promoting knowledge about pharmacogenetics in Europe*

This can be done by a web-based approach with the aim of making pharmacogenetic/genomic activities more visible both within the European and international scientific communities. The website would provide:

- information on location and expertise of different researchers in the field, as a spur to encouraging collaboration;
- a European database complementing the PharmGKB database for Europe-specific features;
- a focal point of organisation of workshops and conferences in specific areas, to encourage researchers to exchange ideas and strengthen and initiate European collaboration.

9.2. *To provide a mechanism for sharing and extending existing research, databases and bio-banks within and outside Europe*

Specifically, this would include:

- promoting the need for performing larger studies to provide evidence for the value of genotyping that stands up to both rigorous statistical and clinical scrutiny;
- developing common quality controls and management structures at a European level;
- encouraging the dissemination of pharmacogenetics research throughout Europe, by pairing leading groups with those having less infrastructure, expertise and equipment.

9.3. *To encourage and facilitate input from and collaboration with the pharmaceutical industry both within and outside Europe*

It was felt that it is essential to integrate the efforts of academia, industry and the regulatory field in Europe to address common issues around pharmacogenetics/genomics. These include ethical and scientific aspects, as well as examination of the ways in which information can be shared without compromising intellectual property and commercial sensitivity.

Specifically, integration should seek to:

- extend inclusion of key individuals from, academia, industry and the regulatory authorities within the management of the network;
- explore ways of improving interaction at the level of exploratory and pre-competitive industrial research, which would lead to new and wider therapeutic opportunities and underpin developments in mechanistic toxicology and safety;
- initiate and establish focused consortia to study disease-specific topics in pharmacogenetics/genomics.

9.4. *To improve education and training in pharmacogenetics/genomics*

This is important, at two levels—the development of a future European cadre of experts in pharmacogenetics/genomics, and the dissemination of information on the subject to users and beneficiaries of pharmacogenetic research, at the level of clinical practice and utilisation. Specifically, it should aim to:

- identify existing courses on pharmacogenetics/genomics within Europe on the website, with a view to publicising their availability throughout Europe; and
- harmonise and improve education and training in pharmacogenetics/genomics, at both undergraduate and postgraduate levels, with an emphasis on the practical implications of the subject.

10. Conclusions from the workshop

There was broad support for starting up a European Pharmacogenomic Initiative and Network, and for using this network as a communicating body with the European Commission. If funding is obtained, a website will be launched (and maintained) and meetings for the participants in the network will be organised, among other things. Collaborations within Europe will develop if there is a platform where researchers can meet and discuss their ideas and initiate new and joint projects. The future of pharmacogenetics/genomics research will be much brighter with the presence of a funded European Network.

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