Symposium of the Paul Martini Foundation in Halle/Saale (Germany) on September 7, 2002

on the occasion of the joint autumn meeting of the (German) Society for Biochemistry and Molecular Biology (GBM) and the German Society for Experimental and Clinical Pharmacology and Toxicology (DGPT)

Pharmacogenomics: Promises and Expectations for Drug Therapy and Drug Development

Michel Eichelbaum (Dr. Margarete Fischer-Bosch-Institute for Clinical Pharmacology Stuttgart, Germany) welcomed over 100 participants to this Paul Martini Symposium, at which the Hans J. Dengler Prize was also awarded.

In his introduction, he pointed out that there is still a great need for new drugs, as there is no adequate treatment for many of the 30,000 known diseases or the available drugs exhibit very uneven response rates because of the genetic variability of the patient population.

70 to 80 % of all new drugs in clinical development have to be abandoned. The most important goal of the application of pharmacogenomics/genetics is to develop effective drugs for the most important diseases, with good response rates, to determine the appropriate dosages of these drugs and, as far as possible, to avoid severe side effects.

André Reis (Friedrich-Alexander-University of Erlangen-Nürnberg, Germany) described in his lecture 'Understanding the genetic basis of common human diseases and its potential for new concepts in drug therapy' the rapid progress in the identification of genetic defects: while only 1,430 such defects were discovered between 1991 and the start of 2001, this number had increased to 1,790 by April 1, 2002.

In recent years, the genome of yeast (1997; about 6,000 genes), the nematode *C. elegans* (1998; about 18,000 genes), the fruit fly (2000; about 13,000 genes) and the mouse-ear cress Arabidopsis (2000; about 35,000 genes) have been decoded to aid the identification of all human genes, and thus the explanation of genetic disorders. Splicing, variation effects at the protein level and post-translational modifications compensate for the relatively low number of genes in the human genome, estimated at 35,000. Single nucleotide polymorphism (SNP) occurs at a frequency of 1 SNP about every 1,000 base pairs and can be the cause of illnesses. This is the case with e.g. the factor-V disease mutation, which leads to increased blood coagulation. By contrast, common diseases such as diabetes, epilepsy, hypertension, asthma, schizophrenia, atopic dermatitis, psoriasis, multiple sclerosis and tuberculosis, as well as having a genetic component of varying importance, also involve other factors. This has been demonstrated in detailed studies with twins. For example, the cause of atopic dermatitis, which has a prevalence of 10–15 % in the population, is 80 % genetic. An EU-wide multi-center study, GENUFAD, identified a corresponding gene on chromosome 3.

Because of the difficulties that have occurred in association studies, new strategies are now being pursued. For example, haplotypes are now investigated instead of SNPs and genome-wide association studies. Reis et al. cited the following consequences for pharmaceutical development:

- There is no golden target.
- The pathophysiology needs to be investigated in great detail.
- The increasing individualization of medicine can be expected to lead to fragmentation of the market.

Klaus Peter Koller (Aventis Pharma in Frankfurt/Main, Germany) described the problems involved in the identification and validation of potential drug targets (proteins, enzymes, metabolites, RNA/DNA) in his lecture 'Genome-wide search for disease genes as new drug targets'. It had been hoped that the answer to the fundamental problem of the pharmaceutical industry – a decreasing output of new active substances despite increasing investment in R&D – would be found partly in pharmacogenomics/proteomics. However, researchers were very quickly confronted with new problems: genome projects produce a large number of possible targets and protein-coding genes of unknown function which, because of the high cost of screening drug candidates, first require laborious validation. Another problem is the lack of availability of tissue banks and the different vocabulary of pathology.

In terms of new developments, he described the use of short double-stranded RNA for the destruction of messenger-RNA, which has advantages over antisense oligonucleotides (lower concentration, substantially longer half-life) and the use of aptamers (selective protein traps).

Of the 200 drugs with the largest turnover in 1997, most targeted a 7G-protein-coupled receptor. As a practical example of the search for targets at Aventis, he mentioned osteoarthritis, which affects 4 million patients in Germany alone. Compilation of gene profiles of patients initially revealed 270 genes that might be involved, but more detailed examination reduced this number to about 50. These are currently under further investigation.

Finally, he pointed to the major importance of national and international networks (e.g. with academia, non-university research institutions, biotech start-up companies), without which it would not be possible to solve the problems facing pharmaceutical companies.

Werner Kroll (Bayer Corporation, West Haven, USA) first discussed in his lecture 'High throughput gene expression profiling to screen for drug effects and toxicity' the urgent problems of research-based pharmaceutical companies: according to one study carried out by the Boston Consulting Group in 2001, the development of a new pharmaceutical now costs US-$ 880 million and takes 14.7 years. 70–80 % of development candidates are abandoned during the clinical phase, about 35 % of them because of lack of efficacy, 35 % because of safety problems and 10 % because of economic considerations.

He then described attempts to use toxicogenomics early and in parallel with development to help avoid the failure of development candidates, especially in the later phases of clinical development, and thus reduce development costs.

While investigations with drug candidates on hepatocytes have shown that they can influence up to 13,000 genes, this large number can ultimately be reduced to about 750. It is advantageous that toxicogenomic tests can be carried out with small quantities of substance (less than 1 mg) and in a short period (approx. 2 days). The studies carried out so far are promising, as it has been possible to assign around 80 % of substances to one of the two categories 'acceptable hepatocyte toxicity' or 'unacceptable hepatocyte toxicity'.

The general objective of pharmacogenomics is ultimately the gene-based diagnosis of diseases and causal treatment. As examples of pharmacogenomics-based pharmaceuticals already on the market, he cited trastuzumab and imatinib.

After that, he talked about the FDA workshop 'Pharmacogenomics/genetics in Drug Development and Regulatory Decision Making' held in May 2002, in which the FDA displayed interest in these new methods.

In the future, he expects that:

- definitions of diseases will be based on mechanisms, not on symptoms
- diseases that are currently homogeneous will become heterogeneous and
- instead of universal drugs (one fits all) more individualized therapies will be developed.

Michael Zühlsdorf (Bayer AG, Wuppertal, Germany) said in the introduction to his lecture 'Pharmacogenomic-based clinical trials to improve drug development' that the 500 targets known so far could increase to 3,000 or 5,000 (and possibly even 10,000) as a result of genome research.

The response rate to pharmaceuticals currently varies widely, ranging from 25 % in oncology to 80 % for more recent antirheumatics.

Strategies to solve the problems facing the pharmaceutical industry (declining/stagnating number of NMEs (new molecular entities); increasing R&D costs; widening disparity between turnover and R&D costs) involve:

- validated new targets
- early identification of drug candidates worth evaluation
- optimization of development times
- early testing of drug candidates with the aid of biomarkers or surrogate markers
- mechanistic understanding of action mechanisms
- identification of genetic markers and effects of alleles on the absorption, distribution, metabolism and excretion of active ingredients, as well as the safety and efficacy of active ingredients.

He attached great importance to biomarkers, as they permit, among other things, very early proof of concept.

The identification of suitable target populations can often substantially reduce development times and costs. For example, a response rate of 10 % would require a clinical study with 7000 patients over 12–18 months and would cost US-$ 70 million, whereas at 50 % the number of patients would be reduced to 300,

the duration of the study to 3 months and the cost to US-$ 1.5 million.

An early example of pre-selection of possible responders accelerating pharmaceutical development, is trastuzumab, to which about one-third of the 25 to 30 % of breast cancer patients with hyperexpression of the HER2 receptor respond. The HIV product containing the active ingredient abacavir, to which 5 % of patients display hypersensitivity, could become another example. In this case, genetic analysis of 200,000 SNPs to identify the genes responsible is being considered.

Zühlsdorf argued that pharmacogenomic/genetic studies should already be taken into account in clinical studies or that blood samples should at least be frozen. They could then be tested at a later date, when genotyping has become cheaper or understanding of individual variability has increased. However, a declaration of informed consent meeting the official requirements would be a prerequisite. The critical points in this regard would be the confidentiality of data; the right to know or not to know; the possibility of information being passed to family members; that information would not be passed on to insurance companies or employers and the question of where and for how long samples would be stored and whether they should be rendered anonymous.

It is expected that pharmacogenomics/genetics will help to identify subpopulations, determine appropriate dosages and enable fixed combinations with specific inhibitors to be developed.

At present, a change in paradigm is taking place in pharmaceutical development, characterized by the following developments: early testing of development candidates with the aid of biomarkers, use of all available data for modeling and simulation studies, rapid proof of concept, rapid development of similar pharmaceuticals to the point of proof of concept and parallel implementation of the different research and development processes.

In summary, he expects pharmacogenomics/genetics to have the following effects:

Research: Estimation of toxicity, metabolism and the response rate

Development: Genotyping of patients, minimization of side-effects, maximization of the response rate

Treatment: Expansion of the available methods of diagnosis, re-definition of diseases, individualization of treatment

Dan Roden (Vanderbilt University of Nashville, USA) in his lecture 'Implementing pharmacogenomics to improve drug therapy: where do we stand in 2002' first presented a short retrospective look at the origins of pharmacogenomics/genetics (first description of pharmacogenetics as an area of research in a book by Prof. Werner Kalow in 1962) and an overview of the many different definitions of pharmacogenomics/genetics, which have now led to the situation where these two terms are either used synonymously or are grouped together as 'pharmacogenics, PGx'.

Pharmacogenomics/genetics is particularly important in the case of pharmaceuticals with narrow therapeutic ranges, e.g. cancer therapy or antiarrhythmics. However, after all the enthusiasm about the initial success of clinical pharmacogenetics it must not be forgotten that the associations between genes and illnesses do not establish causality, so they must be validated in detail. Nor must the influence of the environment be underestimated: 'Genes load the gun, the environment pulls the trigger'. Despite the flood of data about the influence of specific DNA polymorphisms on the efficacy and safety of drugs, there are so far only a few examples of the use of genetic tests before a specific drug is prescribed. Roden illustrated the many and diverse problems and difficulties that have so far prevented widespread use of this concept on the basis of examples (antiarrhythmics; increase in the QT-interval). It is important to keep samples from participants in clinical studies to permit the clarification of questions or problems that come to light later. He, too, discussed the associated ethical problems.

In addition, he described strategies for determining the role of genetics in reactions to drugs.

After a lively discussion where many aspects were raised and clarified, Dieter Götte, spokesman of the Board of the Paul Martini Foundation, thanked all the speakers for their presentations and the audience for their contributions and closed the symposium.