



Federal Ministry
of Health



Pharmaceutical Innovation:

Possibilities and Limits of Personalised Medicine

Dossier

Bonn, Germany, 11 - 12 June 2007



About this publication:

In the framework of the German EU Council Presidency, the Federal Ministry of Health and the Federal Institute for Drugs and Medical Devices were holding in Bonn, on 11th and 12th June 2007, an expert conference on *Pharmaceutical Innovation – Possibilities and Limits of Personalised Medicine*. It was financially supported by the European Commission.

The Conference aimed to intensify a sustainable networking among the participants and develop robust concepts for the future design of pharmaceutical research and production within the EU. To this end, various stakeholders from the fields of pharmaceutical research, production and licensing were brought together.

This publication summarises the main results of the conference. It may reflect the personal views of the individual contributors and is not necessarily the perspective of the Federal Ministry of Health or of the Federal Institute for Drugs and Medical Devices.

Joint Publishers:

Federal Ministry of Health

Friedrichstr. 108

10117 Berlin

Germany

Federal Institute for Drugs and Medical
Devices

Kurt-Georg-Kiesinger-Allee 3

53175 Bonn

Germany

Scientific coordination: Dr. Stephan Brandt

Scientific coordination: Dr. Susanne Keitel

Status: June 2007

This Dossier has been published in:

Bundesgesundheitsblatt – Gesundheitsforschung – Gesundheitsschutz 2008, Volume 50
Issue 6, Pages 675-688.

Table of Contents

Table of Contents	3
I. Introduction (Dr. Thomas Sudhop)	4
II. Workshop 1: Regulatory Affairs (Dr. Birka Lehmann)	7
III. Workshop 2: Cardiovascular Diseases (Dr. Norbert Zimmermann)	12
IV. Workshop 3: Psychiatry/CNS Disorders (Dr. Karl Broich)	16
V. Workshop 4: Haematology/Oncology (Dr. Rembert Elbers)	20
VI. Workshop 5: Metabolic Syndrome/Diabetes (Dr. Martina Weise)	24
VII. Workshop 6: Virology/Immunology (Dr. Regine Lehnert, Dr. Michael Pfeleiderer)	28
VIII. Workshop 7: Undesirable Effects/Toxicology (Dr. Peter Kasper)	32
IX. Summary and Future Prospects	34

I. Introduction

Personalised Medicine

In previous eras of medical research, a common approach focused on cure-all medicinal products, e.g. broadband antibiotics that cover nearly every bacterial infectious disease or analgesics suitable for every type of pain. Initially, the 'one-fits-all' approach appeared to be a smart concept but it has also drawn attention to the fact that every individual may react differently to a medicinal product. While a specific medicinal product may offer the best possible efficacy and safety to an individual person, it may not have a sufficient effect on another person suffering from the same disease, or may even cause harm.

Therefore, **personalised medicine** can be defined as patient-specific application of medicinal products subsequent or in parallel to diagnostic investigation which is performed on the genetic, molecular or cellular level.

From Populations to Individuals – The Role of Genes

Genetic variations are the reason for differences between individuals. They are also responsible for the fact that humans differ in their response to medicinal products as a rule. Reasons for the differences observed are variations in the absorption and distribution of medicinal products and their metabolism, on the one hand, as well as differences in pharmacodynamic efficacy, on the other hand. While for many medicinal products the inter-individual variability is not clinically relevant, it may lead to increased toxicity or to decreased clinical efficacy in some cases.

Pharmacogenetics aims at developing means of optimising medicinal product therapy with respect to the patient's genotype. It deals with the influence of genetic variation on drug response in patients by correlating gene expression or single-nucleotide polymorphisms with a medicinal product's efficacy or toxicity. However, pharmacogenetics tries to ensure maximum efficacy with minimal adverse effects. Such approaches promise the advent of 'personalised medicine', in which medicinal products and medicinal product combinations are optimised for each individual's unique genetic make-up. An individual's response to a medicinal product may be linked to these DNA variations.

The role of metabolising enzymes and transporters within the **pharmacokinetics** of certain medicinal products can be identified. Thus, the interactions of active ingredients as well as the influence of genetic variations can be predicted. Nowadays, by means of a simple blood test it is possible to identify so-called slow metabolisers – subjects with a deficient gene in a

certain metabolic pathway. These 'slow metabolisers' are prone to severe incompatibility reactions to active ingredients that are mainly metabolised by this particular metabolic pathway. By testing and identifying such individuals, serious adverse reactions can be avoided. However, not only deficient genes can be identified. There are also subjects who have more copies of a certain drug-metabolising gene than usually observed. These so-called 'rapid metabolisers' need a higher dosage of certain medicinal products to achieve the same reaction. With the new genotyping techniques, it has become easier to screen large numbers of gene *loci* and also large numbers of patients.

In contrast, **pharmacogenomics** is the broader application of genomic technologies to the discovery of new active ingredients and further characterization of licensed medicinal products. It aims to assign new medicinal products to specific populations in drug research and development. It focuses on the investigation of variations of DNA and also of RNA characteristics. To this end, it combines traditional pharmaceutical sciences such as biochemistry with new, high through-put genotyping technologies. These modern molecular genetic technologies, such as DNA microarrays (gene chips) and many others, have dramatically increased the research through-put. Essentially, pharmacogenetics is one component of pharmacogenomics.

Susceptibility to certain diseases can be influenced by common DNA variations. Therefore, currently, much of the research in pharmacogenomics is focused on genes encoding either metabolic enzymes, which can alter a medicinal product's activity, or defective structural proteins, which result in increased susceptibility to disease, with a particular emphasis on improving medicinal products' safety. Many genes have become the focus of interest and their role as biomarkers is being discussed intensely. While it becomes increasingly easier to find genetic variations, the role of these variations still needs to be clarified. Only clinically relevant biomarkers are helpful in the **development of new medicinal products** and it is one of the future challenges to identify them.

Paediatrics and Geriatrics

Besides genetic differences there are more reasons to differentiate between special patient groups: One reason is the patient's age. In most cases it is not enough to adjust the dose according to the child's body weight since **children** cannot merely be considered as small adults. Special attention must be paid to differences in physiology, **pathophysiology**, pharmacology, pharmacokinetics, and many other factors. This may result in specific paediatric formulations and special paediatric treatment concepts including special paediatric

drug research and development programmes such as the European projects PENTA¹ and TEDDY². Similar issues have also become apparent for **geriatric patients**. Changes in physiology, pharmacology, and pharmacokinetics due to changes in organ functions, body composition, and other changes which are more or less age-related and/or due to accompanying diseases, require adapted treatment concepts for this special population. Since it is generally accepted that special populations might require additional concepts during drug development, regulatory bodies such as the Food and Drug Administration (FDA) or the European Medicines Agency (EMA) issued specific documents to provide scientific guidance covering these areas. Furthermore, regarding medicinal products for paediatric use, Regulations (EC) Nos. 1901/2006 and 1902/2006 were recently implemented within the EC ensuring safety, high quality and efficacy of medicinal products for this target group.

Gender and Ethnicity

Although it is believed that women and men generally react in a comparably equal manner to medicinal products – except for gender-specific diseases – recent research has shown that at least in some common disorders such as cardiovascular diseases, relevant **gender-related differences can be detected which affect diagnostic as well as treatment concepts**. This raises several questions: are women appropriately represented in clinical trials and clinical development programmes? Are the diagnostic measures appropriate to detect possible gender-related differences? Is it necessary to develop special diagnostic and treatment concepts for men and women? The regulatory bodies also acknowledged the recent findings and published first discussion papers to address these possible issues. Although Directive 2001/20/EC³ does not particularly state criteria for gender distribution in clinical trials, the relevant EC Guidance Document⁴ rules that applications to Ethics Committees should consider special trial populations. In this respect the German GCP-Regulation⁵ and a guidance document⁶ published by the German authorities, the Federal Institute for Drugs and Medical Devices and the Paul-Ehrlich-Institute, explicitly stipulate explanations regarding gender distribution. However, the situation with regard to ethnic differences is even more complex. Although politically not always easy to deal with, there are

¹ Paediatric European Network for the Treatment of AIDS

² Task-Force in Europe for the Drug Development for the Young

³ Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

⁴ ENTR/CT2 Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use.

⁵ Article 7 paragraph. 2 no. 12 of the "Verordnung über die Anwendung der Guten Klinischen Praxis bei der Durchführung von klinischen Prüfungen mit Arzneimitteln zur Anwendung am Menschen".

⁶ No 1.1 3. Bekanntmachung zur klinischen Prüfung von Arzneimitteln am Menschen. Joint notification by the German Federal Institute for Drugs and Medical Devices and the Paul-Ehrlich-Institute.

several ethnic differences from a medical and physiological point of view which lead to treatment consequences in different areas of the world. With the first ethnic-specific marketing authorisation for a combined nitrate/diuretic product for African Americans in the USA, the FDA has reacted to the different results of clinical trials demonstrating ethnic differences.

Conclusions and Outlook

The enhanced predictability of individual risk profiles based on genetic sampling also emphasizes the role of data protection and raises concerns regarding certain ethical aspects still under discussion. Although there are many open questions in personalised medicine concepts, it becomes obvious that personalised medicine will play an important role in drug development as well as in the treatment of patients. There are still many areas where the 'one-fits-all' approach is currently the most suitable treatment concept, but there will be more and more fields in human medicine where a tailored treatment will be the best choice. The pharmaceutical industry, universities, regulatory authorities and even society must be prepared to deal with these new concepts of medical research to identify opportunities as well as risks in order to benefit from the recent developments.

II. Workshop 1: Regulatory Affairs

Legal Requirements

All action in the pharmaceutical sector generally aims at **guaranteeing a high level of health protection** for patients, **harmonising the market access** and **providing overall legal certainty**, while allowing for **sufficient flexibility at technical level**. To this end, legal frameworks exist on all major markets. Within the European Union this framework comprises a series of directives, regulations and conventions (e.g. Directives Nos. 2001/20/EC and 2001/83/EC or Regulations Nos. (EC) 1901/2006, (EC) 1902/2006 or the new Regulation of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004) which has to be **carefully scrutinised to adjust it to the challenges of the new approach** for patients to receive personalised medicinal products by not violating

- the rights and well-being of the individual subject participating in a clinical trial,
- the right of the patient to receive a medicinal product meeting all requirements with regard to quality, safety and efficacy and

- the pharmacovigilance following an approval for the continuous risk-benefit evaluation.

Furthermore, due to the increasing number of pharmacogenomic programmes conducted by the pharmaceutical industry, the regulatory bodies recognised the need for regulatory advice. FDA and EMEA as well as the International Conference on Harmonisation of Technical Requirements (ICH) published several guidance documents on various aspects of pharmacogenomics. Recently, these concept and reflection papers have been focused more and more on medical specialties such as oncology or cardiovascular diseases emphasizing the **prospective role of personalised medicine** in the development of medicinal products.

Regulatory Requirements

Diagnostics based on pharmacogenetics is still not a mandatory requirement for the development of medicinal products and it has to be carefully considered whether this approach should become a 'catch all' requirement. Study designs of many pharmacogenetic trials are inadequately designed for drawing conclusions applicable to clinical and regulatory practice. To date, **genetic biomarkers have rarely been incorporated** in well-controlled late phases of clinical trials for the purpose of a proactive patient selection or patient stratification. Application of pharmacogenetics-based diagnostics in therapeutic decisions would be facilitated if pharmacogenetic analyses were already included in the clinical studies during the development of drugs, but currently this diagnostic approach is still far from being applied in general clinical practice.

It is necessary to **define the data** which will be **required for marketing authorisations of medicinal products** and **to explain how to get these data**. These could possibly include:

- laboratory techniques and test procedures and standardized assays;
- definition of 'state of the art' for interpreting the physiological, toxicological, pharmacological, or clinical significance of specific experimental findings;
- definition of various human (sub)populations with different genetic backgrounds;
- design of clinical trials, e.g. various kinds of response among different genotypes, prevalence of relevant genotypes in the population or interaction of genetic factors with environmental factors;
- some pharmacogenetic tests – primarily those related to the metabolism of medicinal products – which have well-accepted mechanistic and clinical significance and are

currently being integrated into decision-making and clinical practice in the development of drugs.

Ethical Aspects

The **developments in genetics pose ethical questions** for individuals and society. Personalized medicine presents new challenges, especially regarding the ethical principles of autonomy and justice. Benefits for the individual and the health care system ought to be balanced against the risk of discrimination. Part of this challenge is the application of ethical principles regarding data protection. Considerations should include aspects of equal and fair access to diagnostic and therapeutic services and standards of quality, safety and the efficacy of the respective instruments. As the field progresses rapidly, ongoing research and public debate are needed to provide the lawmaker with the requisite input for legislative action.

How could pharmacogenetics affect the way medicine is practised today?

Currently, physicians prescribe medication through a trial-and-error method of matching patients with the right medicinal products. If the prescribed medication does not work for the patient the first time, the physician will try a different drug or dosage, repeating the process until the patient's health improves. As pharmacogenetics becomes more advanced, physicians eventually will be able to prescribe medication based on an individual patient's genotype, maximizing effectiveness while minimizing side effects.

Anticipated Benefits of Pharmacogenetics

Pharmacogenetics will finally provide a tailored medicinal product therapy based on genetic determinants related to improved efficacy and reduced side effects. This may result in possible benefits for at least three groups:

The patients

- **More powerful medicines:** Pharmaceutical companies will be able to produce therapies more targeted to specific diseases and maximizing therapeutic effects.
- **Better, safer medicinal products:** The period of recovery will be reduced and safety will be improved as the likelihood of adverse reactions decreases or is eliminated altogether.
- **More accurate methods of determining appropriate medicinal product dosages:** Current methods of dosages determined by weight and age will be replaced by dosages based on a person's genetics - how well the body metabolises the medicine.

- **Confidence:** the physician's confidence in prescribing a medicinal product and the patient's confidence in taking it will be increased.
- **Better vaccines:** With the help of vaccines made of genetic material, be it DNA or RNA, one can expect to benefit from the advantages of existing vaccines without having to cope with many of their risks. From a theoretical point of view, they could stimulate the immune system but might not trigger any infections.

The pharmaceutical companies

- **SNP screenings will benefit the development and testing of medicinal products** because pharmaceutical companies could exclude those persons from clinical trials whose pharmacogenetic screening would indicate that the medicinal product being tested would be harmful to them or ineffective in their case. By excluding these people, the chance will be increased that a medicinal product will prove its usefulness for a particular population group. Thus, the likelihood will be increased that the same medicinal product reaches the market, although for a stratified population only.
- The number of failures in medicinal product trials will decrease due to optimised patient stratification.
- **Pre-screening clinical trial subjects** should also allow the clinical trials to be **smaller, faster, and therefore less expensive**; consequently, the consumer could benefit from reduced costs for medicinal products.
- **The ability to assess an individual's reaction to a medicinal product before it is prescribed** should encourage the development of new medicinal products tested likewise.

The society/the health care system

Pharmacogenetics may finally lead to an **overall decrease in the cost of health care** by reducing

- the number of adverse reactions to medicinal products,
- the gap between 'research and development', and market entry of pharmaceutical innovations,
- the duration of therapy,
- the number of medicinal products patients must take to find an effective therapy, and
- the disease burden, through early diagnosis and adapted therapy.

Difficulties and Drawbacks of Pharmacogenetics

There have been explicit concerns about the commercialisation of genetic testing because of doubts about the adequacy of **pre-test information** and **counselling**, which are essential for informed consent, and of **post-test counselling** and **support**, especially when tests will determine the susceptibility to a disorder. Commercialisation affects private and public laboratories. There is also unease that economic issues will trigger aggressive marketing of genetic tests. Thus, the availability of valid tests may differ significantly depending on the different interests of development.

Further to the assumption set forth in the above section on 'economic benefits', it is much too early to give a definite statement on the future costs of personalised medicines. This would have to take into account the costs of research, including significant clinical trials, development of diagnostic kits for determination of the 'right' patients or patient groups as well as applying personalised medicine in clinical practice. Particularly the development of diagnostic kits will be even more difficult when complex diseases caused or influenced by more than a single gene are to be analysed.

To date, **numerous potential genetic biomarkers have been identified but few of them could be definitely established**. What is still lacking is the comprehensive validation of genetic variants which may be associated with diseases or therapies on the basis of evidence-based scientific studies. The reason for this is the complexity of conducting clinical trials which sufficiently respect the possibilities of other important factors, e.g. ethnical differences.

Laboratories may be tempted to rely on health professionals for receiving the required information, counselling and support services at a time when the level of professional knowledge about genetic testing is insufficient, and when there is a shortage of trained counsellors, especially in primary care. Therefore, it is a basic requirement to inform and educate physicians regarding the possibilities and limits of this new approach towards the treatment of patients with a well-diagnosed disease.

Access to the gene/genomic information of an individual patient or a group of individuals should be considered with utmost care. Special attention has to be paid to the **protection of personal rights and data**. Discrimination and stigmatisation have to be prohibited. Consequently, employers or insurance companies, for example, should not have access to these data.

Last but not least, it still has to be kept in mind that the complexity of the dynamics of human health and diseases is not just a ‘problem of translation’ between genotype and phenotype. ‘Geneticisation’ or ‘genetic determinism’ of the perception of human beings as essentially consisting of their genes and being describable in the language of genetics, i.e. the view that human behaviour and health are pre-determined by people’s genetic make-up - or especially naïve forms of this view - raises major concerns. The **concentration on research on genes and their health implications could lead to neglecting the effects of other factors on human health**, such as the physical, social and economic environments in which people are living.

Conclusions and Outlook

It has been recognised that the advent of personalised medicine is a challenge to existing legal frameworks. In some cases, existing legal regulations require revision, in others, it is necessary to enact new regulations. It has to be carefully considered whether the changes in the legal and regulatory framework are supporting the research and development of personalised medicinal products (incentives) or are setting new standards for the marketing authorisation of medicinal products. However, at least two aspects have to be considered – easy access of patients to high quality advanced therapies as well as patients’ rights and safety. In terms of regulatory requirements, it is important to define, on the one hand, which data are required for the marketing authorisation of a medicinal product and, on the other hand, how these data have to be collected. For both, legal as well as regulatory requirements, ethical aspects must be considered. If all these criteria are met, pharmacogenetics could change medicine as it is practised nowadays, although some possible disadvantages are to be expected.

III. Workshop 2: Cardiovascular Diseases

Cardiologists are confronted with patients receiving a multitude of medications. Concurrently, drug effects become increasingly variable, reflecting interaction between individual medicinal products and differences between the respectively underlying diseases. Hence, the knowledge of diagnostic results as well as drug action and drug interaction in the individual patient is crucial in order to find the safest and most effective therapy.

An increasing number of examples describing differences in drug response as a result of genetic polymorphisms have been published, but most of these reports lack explicit

statements on how to make use of this information in clinical drug therapy. Specific, feasible and straight-forward clinical recommendations on how to individualize cardiovascular medication are essential in order to improve drug therapy, particularly in active ingredients with a narrow therapeutic range.

Especially gender-specific and ethnic features may influence the efficacy and safety of cardiovascular medicinal products. Modern techniques such as genetic testing and nanotechnology might help to optimize diagnosis and facilitate individual drug treatment.

Gender and Cardiovascular Disease

The cardiovascular system is regulated by many complex neurohumoral mechanisms which ensure the optimal cardiac, cerebral and renal function. The neural control of the heart is mainly mediated by the vagal and sympathetic systems and by their interaction, known as the **sympatho-vagal balance**. Differences in this balance have been described between men and fertile women. Moreover, an increased sympathetic tone is found in different abnormal situations, such as chronic heart failure and myocardial infarction and this is associated with an increase in overall mortality.

It has also been shown that men respond to **psychological stress** with higher levels of cortisol as compared to women. This greater activation of the hypothalamic-pituitary axis could result in an elevated risk of cardiovascular disease (CVD) and may be linked to the higher prevalence of these diseases (e.g. hypertension) in men.

Symptoms of heart diseases may also be gender-specific. In fact, women more often experience nausea and back pain during a heart attack, while men tend to have left arm pain and chest pain, which are both considered to be the 'classic' symptoms of a heart attack. According to the 'EUROPEAN HEART SURVEY' there are significant differences between male and female patients with established **coronary artery disease** in the frequency of major cardiovascular events which might be due to differences in the use of angiography and in the treatment with anti-platelet or lipid-lowering drugs.

Gender-related differences in the clinical effects of major cardiovascular drugs have been identified, for example, digitalis, beta-blockers, angiotensin-converting enzyme inhibitors and diuretics. Moreover, there are several pharmacokinetic differences in the ways in which women and men metabolize drugs. These discrepancies are based on differences in drug absorption or metabolism, and are frequently related to the cytochrome P450 (CYP) system.

Given the knowledge of the role of gender in cardiovascular diseases and its treatment, a systematic search for gender-related differences in the pharmacodynamics and pharmacokinetics of drugs should be integrated into all phases of drug development, from preclinical studies throughout all stages of clinical trials.

Ethnic Background

In 2005, the FDA approved a drug for the treatment of **heart failure** in self-identified black patients. This drug is reported to be the first medicinal product aiming at a specific racial group and has caused a debate about the future of personalised medicine.

Although there are some ethnic differences, the overall evidence for ethnic variations in response to cardiovascular medicinal products seems to be modest. Some examples may illustrate this item:

- Compared with white patients, black patients were found to respond less to **angiotensin-converting enzyme inhibitors (ACE inhibitors)**. In general, ACE inhibitors are apparently less effective in lowering blood pressure in black people than in white people, possibly because of a higher prevalence of states of low-renin concentration in the black population suffering from hypertension.
- **Diuretics** were found to be beneficial for both black and white patients with heart failure.
- Black patients were found to respond equally well to **spironolactone, digoxin, and carvedilol** (β -adrenoceptor-antagonists).
- It was reported that Chinese patients require lower dosages of some **anticoagulants** (heparin, warfarin) than those usually recommended for white patients.

Due to ethnic differences in cardiovascular diseases, specific research on existing drugs and specific strategies in the development of novel active ingredients seems reasonable. A comprehensive approach is necessary to understand the entirety of the ethnic-related differences. This should include their genetic basis and gene-environment interactions throughout all developmental stages to optimize pharmacological therapy for patients with different ethnic backgrounds.

Genetic Testing

Genetic variability may influence pharmacokinetics, efficacy, and side effects of cardiovascular medicinal products. This is demonstrated by the following examples:

- Genetic variability in the transport protein **MDR-1** influences plasma levels of digoxin, an active ingredient with a narrow therapeutic range used in patients with heart failure.
- Polymorphisms in drug metabolizing pathways, like the **cytochrome P450 enzyme family (CYP450)**, are of major importance. A member of this family, CYP2D6, is responsible for the metabolism of many cardiovascular active ingredients (beta-blockers, antiarrhythmics). 7 - 8 % of the population are 'poor metabolisers' and may require lower dosages to achieve the same therapeutic effect due to lower enzymatic activity and they experience more side effects with the same dosage of the medicinal product.
- Human cardiac arrhythmias are known to arise from dysfunction of the **ion channels** that contribute to cardiac action potentials. Genetic variants due to which patients are predisposed to acquire arrhythmias have been identified. Moreover, life-threatening arrhythmias (Torsades de pointes) have been linked to polymorphisms in ion channel-genes.

With the advances of technology in genetic and genomic testing, genotyping may become easily accessible in future. This approach, integrating genotype-phenotype relation and other individual characteristics both in clinical studies and in an individual patient, may be a useful tool for improving drug therapy. Ethical considerations arise with knowledge about an individual genetic pattern. Among these are the possibilities of hitherto unknown future information about an association of a genetic pattern with diseases.

On the basis of pharmacokinetic data and clinical data on drug effects, CYP genotype-based dose recommendations can be derived for only a few drugs.

As in most other areas of pharmacogenetics, the concept of therapy based on genotype has not been evaluated prospectively in a randomized controlled clinical trial in which one arm was dosed according to genotype and the other treated as usual. In the current era of evidence-based medicine, and with the increasing consideration of pharmacoeconomics in medicine, it is unlikely that CYP genotyping will become routine clinical practice unless its value is demonstrated by such rigorous evaluations. Such studies may, however, be justified for drugs with a narrow therapeutic index.

Nanotechnology

Nanotechnology is seen as a potential future **key technology** with an important impact on medicine. Nanoparticles may play a role in the transport of active ingredients or genes into

cells, selection of cells, growth of stem cells, optimisation of the interaction between implants and tissue, and imaging techniques using nanoparticles as contrast agents. In cardiovascular medicine, imaging techniques may be used to improve risk assessment and to detect inflammatory alterations in vessels due to which the patient may be predisposed to occlusion of vessels and myocardial infarction.

Antiangiogenic paramagnetic nanoparticles may be used to serially assess the severity of atherosclerotic disease in asymptomatic, high-risk patients by detecting the development of plaque neovasculature, which reflects the underlying lesion activity and vulnerability to rupture. The nanoparticles can locally deliver antiangiogenic therapy, which may acutely retard plaque progression, allowing aggressive statin therapy to become effective. Moreover, these agents may be useful as a quantitative marker to guide atherosclerotic management in an asymptomatic patient. In those cases, if the patient is transferred to the catheterization laboratory for revascularization, nanoparticles incorporating antirestenotic drugs can be delivered directly into the wall of lesions not amenable to drug-eluting stent placement. Targeted nanoparticles could help ensure that antirestenotic drugs are available for all lesions. Moreover, displacement of antiproliferative agents from the intimal surface into the vascular wall is likely to improve the healing of the endothelium, improving post-procedural management of these patients.

Conclusions and Outlook

Future research will need to look at gender differences, ethnic, genetic and genomic factors that influence the prevention, diagnosis and overall management of cardiovascular diseases. New technological approaches may help to tailor therapies for the specific needs of patients with cardiovascular diseases. In order to establish evidence-based individualized therapy in cardiovascular medicine, a systematic search for individual differences in the pharmacodynamics and pharmacokinetics of drugs should be integrated into all phases of drug development. Moreover, therapeutic guidelines have to be updated concerning individualized therapeutic approaches.

IV. Workshop 3: Psychiatry/CNS Disorders

In psychiatry and neurology, medical history and examination of the patient have been more pronounced key elements of diagnosis and treatment than in other medical disciplines. Historically, two fundamental approaches have been used so far to formulate systems of disease classification, particularly in psychiatry: the etiological and the descriptive approach.

With the advent of the **International Classification of Diseases and Related Health Problems (ICD-10)** and the **Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)** as classification systems it was established that practitioners and researchers communicate more effectively with each other by defining more or less homogeneous patient populations.

The development of ICD-10 and DSM-IV-TR facilitated the identification and management of mental disorders in both clinical and research settings. Despite considerable increases in basic science as well as available experimental techniques, this approach is subject to certain limitations as it is mainly based on subjective reports from the patients and subjective elements in their evaluation by psychiatric experts. Unfortunately, to date there are no specific biological diagnostic markers which are reliable, sensitive and objective and which could be used as 'golden standards of diagnostics' in psychiatric disorders - e.g. **schizophrenia** is highly heterogeneous from a clinical and phenomenological point of view and there is no unanimous agreement on its identity as a disease entity. Quite on the contrary, there are profound discussions as to whether schizophrenia is indeed a distinct type of disease or rather a generic term for a number of probably separate disease entities and this applies to many other psychiatric disorders as well. Thus, on the one hand, schizophrenia is considered to be a very familiar disorder which is strongly influenced by genetic factors and for which several candidate genes have been isolated; on the other hand, none of these genes definitely has a key role in the aetiology of schizophrenia. Nonetheless, for a higher efficiency in genetic investigations in schizophrenia and other psychiatric disorders, a new approach has been developed to define clinically distinct traits much more precisely: the so called endophenotype concept.

A similar research status is found in **Alzheimer's disease** – another multifactorial and complex disease entity. In the primary pathogenic processes, more than 200 different genes, which are distributed across the human genome, are involved. Mutations in genes directly associated with the amyloidal cascade, which reflects the main pathogenetic hypothesis for the development of Alzheimer's disease, are only present in less than 5% of the population of patients with Alzheimer' disease. However, the analysis of genotype-phenotype correlations revealed the presence of the APO E-4 allele as a major risk factor in 40% of patients with dementia. In conjunction with other loci of the human genome, this allele influences the onset of the disease, brain atrophy, β -Amyloid load, apoptosis, lipid metabolism, impairment of cognitive functions and treatment response.

In contrast to this, **hereditary neuropathies** are an example from the field of neurology, where a former clinical-phenomenological classification of diseases has been considerably changed due to major progress in the knowledge of the molecular basis by identifying only a few distinct chromosomal loci or genes involved in a given disease phenotype.

Therefore, many researchers in psychiatry focused on genetics and genomics, particularly within the areas of linkage and association studies, and on gene identification. They hoped that this progress could be translated into nosologic insights which would basically change conceptualization and diagnostic purposes in psychiatric disorders. However, up to now the link between candidate genes and schizophrenia, for example, is rather modest, and much more research, such as on the **concept of endophenotypes**, is needed to elucidate the many positive and often confusing findings that have emerged.

Hopefully, this will lead to an improved delineation of psychiatric disease entities in future. Consequently, extensive research on DSM-V has been initiated to provide studies and data to facilitate the integration of findings from basic research, particularly molecular genetics, epidemiology and clinical research.

Based on current knowledge, the treatment of central nervous system disorders is one of the areas where pharmacogenetic and pharmacogenomic results will probably be applied to improve the outcomes for the patient. Many treatment options in psychiatric patients are only partially effective, e.g. in schizophrenia or affective disorders 25 to 40 % of the patients do not respond to their first applied treatment option, and among those who definitely respond, 10 to 20 % show reactions of clinically relevant adverse effects like sedation, extrapyramidal side effects, weight gain, etc.

The mechanisms causing non-response in patients with neuropsychiatric disorders are not well understood but many variations are probably based on polymorphic genes encoding enzymes (**cytochrome P-450 (CYP)**) that affect the way medicinal products are metabolized.

For antidepressant medicinal products, plasma concentrations in patients who had been given the same dose have proved to vary extremely, some of the levels being even more than 40 times the amount of some others. The clinical relevance of this variability is that with a standard dosage of antidepressant drugs only some of the patients will exhibit active ingredient concentrations in their tissues that are associated with an optimal response,

whereas others will have either low, ineffective active ingredient concentrations or unnecessarily high concentrations which may be poorly tolerated.

Therefore, **therapeutic drug monitoring** can be considered as a promising procedure for many psychoactive medicinal products by preventing dose-dependent adverse drug events, optimizing dosage during long-term treatment and identifying ultra-rapid metabolisers and malcompliance. However, its application in everyday clinical practice is far from being optimal and despite evidence to support its potential benefit (e.g. plasma levels of mood stabilizers, antidepressants or antiepileptics), therapeutic drug monitoring is not sufficiently applied and developed in everyday clinical practice. Clinicians and health care agencies do not adequately appreciate the degree of pharmacokinetic variability found in patients and its possible impact on the individual patient's response to pharmacotherapy. Hence, the perception prevails that therapeutic drug monitoring is an unnecessary, complicated and expensive procedure. However, recent research results do not support this view. Available data do suggest that therapeutic drug monitoring can favourably affect the outcome of e.g. a treatment with antidepressant medicinal products by offering a reasonable alternative to the inherently slower, 'trial and error' practice of dosage titration based on clinical response ('treatment using a dosage as low as possible and as high as necessary, for a period of time long enough to judge the response', which means, e.g. with a standard antidepressant, a treatment period of at least 4 to 8 weeks). Moreover, with the help of pharmacogenetic testing abnormal metabolisers can be identified: Genetic polymorphisms of the drug-metabolising enzymes CYP3A4, CYP2C9, CYP2C19 and CYP2D6 have been characterized, and several of these variants lead to reduced or absent activity, particularly of psychoactive active ingredients. This is of clinical importance mainly in patients who have two non-functional alleles, phenotypically characterised as 'poor metabolisers' (1-10% of Caucasians). Since most active ingredients are transformed into inactive or less active metabolites, 'poor metabolisers' are at an increased risk of developing drug-induced adverse reactions.

In order to interpret the plasma levels accurately, age, gender, ethnicity, compliance, medicinal product dosage, renal and hepatic functions and particularly co-medication including smoking habits and caffeine intake have to be taken into account in most cases when using psychoactive medicinal products. However, it seems unlikely that therapeutic drug monitoring will become a standard of care for all psychoactive agents and all patients as it is currently the case with many antiepileptic medicinal products in patients suffering from epilepsy. Therefore, the question arises: for which psychoactive agents, for which patients and under what circumstances is **therapeutic drug monitoring** more cost-effective than the

traditional dose titration in neuropsychiatric conditions. The application of therapeutic drug monitoring to optimise the efficient use of selected psychoactive agents could potentially improve individual patients' responses and free up health care resources to sponsor other equally deserving treatments.

Conclusions and Outlook

Particularly the role of molecular genetics for understanding neurobiology, signs and symptoms, prognostic factors and response to treatment of psychiatric and neurological disorders is rapidly increasing. Despite these substantial developments and new research data and insights, progress which can be directly translated into benefit for individual patients has not been as rapid due to the enormous complexity of human genome variations in disorders of the central nervous system. Nevertheless, in future pharmacogenomics will have a significant impact on drug research and development for medicinal products allowing of a better identification of genetic drug targets involved in the aetiology of psychiatric disorders, whereas pharmacogenetics taking into consideration genetic polymorphisms of the CYP-P450 system already allows of an improved treatment response and a lower rate of adverse side effects as first steps on the way to a 'personalised' treatment in psychiatry and neurology.

V. Workshop 4: Haematology/Oncology

Introduction

For most forms of cancer and in most individual cases, the exact cause for the disease is unknown. However, it is assumed that cancer can be caused by genetic susceptibility, lifestyle choices, and exposure to certain environmental hazards. Malignant neoplasms are important causes of death in adults, second only in numbers to major cardiovascular diseases. In middle-aged adults (between 45 and 69 years of age), malignancies are even the leading cause of death. For society and for the individual, the medical, psychological, social, and economic burden of cancer can be literally taxing.

While there have been steady and sometimes even dramatic improvements in the therapeutic approaches and in the outcome of these diseases, nobody has yet found a 'magical cure' for cancer, despite numerous claims to the contrary. By its very nature, cancer is a survivor. It has only one purpose: to proliferate. After all, that is the definition of cancer: unregulated growth of cells that take no heed of the message to stop growing. Normal cells

go through a cycle of division, aging, and then selection for death. Cancer cells are able to circumvent this normal cycle, and escape recognition to be eliminated.

Most forms of cancer are still life-threatening. However, strides have been made in the fight against the disease, e.g. in treatment of some forms of testicular cancer or leukaemia in children. Doubtlessly, progress has been made, but more progress is essential.

In recent years the pace of changes in the knowledge about the scientific basis in our understanding of malignant diseases has apparently increased. Advances in molecular biology, genomics, proteomics, signal transduction, and immunology have opened new perspectives towards a more targeted, personalised and individualized future therapy by broadening the understanding of molecular and cellular processes.

Targeted Therapy

Classical pharmaceutical cancer treatment has focused primarily on killing rapidly dividing cells with cytotoxic medicinal products. Unfortunately, some normal body cells divide rapidly, too, causing multiple side effects. Targeted therapy is about identifying cancer cells' specific features. Scientists look for specific differences between cancer and normal cells. This information is used to create a targeted therapy to attack cancer cells without damaging normal cells, thus reducing the range of side effects. Each type of targeted therapy works in a slightly different manner, but all of them interfere with the ability of the cancer cell to grow, divide, repair and/or communicate with other cells.

Cellular signal transmission is involved in vital processes such as cell growth and survival. In cancer cells, mutations are often found in genes underlying cellular signal transmission (for instance, members of the '**Epithelial Growth Factor Receptor**'- (**EGFR**-) family). Therefore, identifying the differences in this process is a representative example and a promising field for targeted therapy: EGFR-related receptors can be blocked from the outside of the cell by certain monoclonal antibodies or from the cellular inside by tyrosine kinase inhibitors. These medicinal products are either able to directly control tumour cell division or they act as anti-angiogenesis drugs by targeting the blood vessels that supply oxygen to the cells, ultimately causing the malignancy to starve.

In recent years, a few new active ingredients that make use of differences in cellular signal transmission have reached the market and also the patients, like e.g. Bevacizumab for patients with metastatic carcinoma of the colon or rectum; Cetuximab for EGFR-expressing

metastatic colorectal cancer or advanced squamous cell cancer of the head and neck. Many other products are still being developed.

Towards Personalised Therapy – Genes

With the arrival of all the new methods and instruments of molecular biology, genes have come into the focus of current cancer research. In particular, strides in the understanding of genetic mechanisms of carcinogenesis and the identification of molecular targets are promising future improvements in cancer therapy. Why are genes emphasized in this way? The reason is that genes are the potential reason for as well as the answer to cancer. Genes regulate some of our micro- and macroscopic processes by coding the proteins which control our structure and function. Through an integrated genomic and proteomic analysis, the ultimate outcome will be an actual functional understanding of the molecular processes that are subject to normal development and disease-related pathophysiology. This higher level of functional understanding will be the basis for an actually reasonable therapeutic design.

For example, Chen *et al.*⁷ reported on a study of gene expression-profiling in the most common form of **lung cancer**, non-small-cell lung cancer. This study exemplifies in a clear form the current possibilities but also the current limitations in genetic cancer research. Chen *et al.* first studied a DNA microarray of 672 previously identified invasion-associated genes. Of these genes, 16 were identified that correlated with an increased (4) or decreased (12) rate of survival. Subsequently, patients were classified according to their risk of death or relapse, based on their expression patterns of these genes. The clinical validation of the newly found genetic predictors showed that the median overall survival was twice as long in the low-risk group as in the high-risk group (40 months vs. 20 months), and there was even a greater improvement in the median survival without progression in the low-risk group (29 months vs. 13 months).

The work of Chen *et al.* reflects the maturation of the first phase of lung-cancer genomics, which has been based on stored tissue and clinical charts. The field is now poised to begin its next phase — conducting prospective trials of adjuvant chemotherapy in patients with early lung cancer who are selected because they have a high risk of relapse or metastasis according to the molecular signature identified by Chen *et al.* or others. Next, cancer genomics will have to expand into two areas: molecular profiles associated with response or resistance to particular standard or advanced therapies and clinical trials based on molecular profiles that indicate a benefit from new or standard agents. However, there is still a long way

⁷ Chen H-Y, Yu S-L, Chen C-H, et al. A five-gene signature and clinical outcome in non-small-cell lung cancer. *N Engl J Med* 2007;356:11-20.

to go until this will enter clinical practice. This new phase of target profiling and agent-specific profiling will probably require an algorithm that would include genomic, proteomic, clinical, and imaging factors.

Better Personalised Therapy – Biomarkers and Cellular Markers

Often only a fraction of cancer patients respond to given cancer therapy, so for a long time research has been seeking to identify biomarkers that could predict response to therapy and thus facilitate the selection of the most appropriate therapy for a given patient. But despite considerable efforts devoted to finding diagnostic markers, progress has been slow. When cells become cancerous, they can release unique proteins and other molecules into the blood and other body fluids or to the surface of cancerous cells. Biomarkers are biological indicators of disease or therapeutic effects, which can be measured through dynamic imaging tests, as well as tests on blood, tissue and other biological samples. Prostate-specific antigen (PSA) is an example for a biomarker which is currently widespread and successfully used to monitor the growth of **prostate cancer**. These markers may include, but are not limited to, genomic, epigenomic, proteomics, cellular and morphologic, and genetic factors by which the patient is predisposed to the disease or which indicate the occurrence or progression of the disease. Identifying protein biomarkers is extremely difficult, however, due to the large number of proteins in the body and the fact that their structures are frequently modified in response to environmental and other stressors in cells. Recent technological advances in biomedical research, especially in genomics and proteomics, have made it easier to identify many new markers of cancer that could potentially improve cancer screening, diagnosis, and treatment. Current and future technologies are expected to be sufficiently robust to discover these proteins and to contribute to an improved individualized cancer therapy.

Conclusions and Outlook

The examples mentioned above are just a few of current cancer research. They are stages on a long path of paradigm change in cancer therapy, starting out from unspecific cytotoxic medicines towards targeted therapies, and hopefully leading to an improved personalised therapy in future. Further promising fields could be added like autologous cancer vaccines, cellular therapies and gene therapy. However, as others have already said, it is difficult to make predictions, in particular with regard to the future, and nobody knows from which field the next breakthrough will emerge. Much more research and more hard evidence will be needed before patients will truly benefit from all those new developments resulting from research into cancer, haematology or immunology. This will require a lot of time, patience

and sufficient funds for research purposes. When new medicinal products will be developed for some future individualized therapy, they will only be useful for a small sub-group of patients suffering from the disease. Under these circumstances, even for rather common types of cancer the benefiting population might become so small, that pharmaceutical industry cannot realistically expect to recover the cost of development. For this situation the public sector has to find additional incentives to ensure that the targeted, individualized cancer therapy which had been promised will finally come true.

VI. Workshop 5: Metabolic Syndrome/Diabetes

Introduction

Metabolic syndrome is an insulin-resistant state characterized by a cluster of cardiovascular risk factors, including various combinations of abdominal fatness, glucose intolerance, high blood pressure, and disturbances in serum lipids known to stimulate atherosclerosis. However, there is an ongoing debate about the definition of the metabolic syndrome and whether this clustering of cardiovascular risk factors is to be considered as a disease in its own right. Although not all patients with such metabolic abnormalities progress to type 2 diabetes, their risk of developing the disease is significantly increased. Lifestyle factors, such as poor diet and a sedentary lifestyle, which in turn lead to or worsen obesity, have a major impact on the risk of developing type 2 diabetes.

Diabetes mellitus is a metabolic disorder characterized by chronically elevated blood sugar levels with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin action (insulin resistance) and insulin secretion (beta-cell dysfunction). More than 90% of patients with diabetes are suffering from type 2 diabetes, also called non-insulin dependent diabetes. Over the past decades, the frequency of type 2 diabetes has drastically increased. Currently, approximately 150 million people worldwide have type 2 diabetes. It is estimated that this number will nearly double by the year 2050. Therefore, we are facing a **worldwide epidemic of type 2 diabetes** representing a major health issue and socio-economic burden.

Risk Factors for Developing Type 2 Diabetes

The pathogenesis of type 2 diabetes is based on multiple factors. Known **risk factors** include genetic predisposition, increasing age, overweight, particularly with abdominal fat distribution, and physical inactivity. Individuals with certain ethnic backgrounds such as native Americans are at an increased risk of developing the disease. Type 2 diabetes used to

be a disease primarily found among elderly people but, due to the obesity epidemics, it is now diagnosed to an increasing extent in adolescents and even in children.

The importance of genetic predisposition in the development of diabetes is undisputed and the identification of **genetic risk factors** is increasingly successful. Genome-wide association studies have confirmed well-known candidate genes such as CAPN10, ENPP1, GCK and HNF4a. To date, the most relevant genes appear to be TCF7L2, SLC30A8 and HHEX. Most of the identified genes play a role in the development or function of beta-cells. The recent discoveries have provided new insights into the pathobiology of diabetes and are of potential interest for a **personalised preventive medicine programme**.

To counter the imminent diabetes epidemics, however, **diabetes prevention** must be the main goal. Given that today's main risk factors for the development of type 2 diabetes are overweight and a sedentary lifestyle, it is not surprising that interventions reversing or improving these factors have been shown to prevent, or at least delay, the progression to type 2 diabetes in high-risk individuals. Although, recently, an 'obesity gene' FTO has been described, and genetic predisposition is likely to play a role in the development of overweight, genetic variants alone cannot explain the world-wide obesity epidemics. Public health strategies are needed to address population-wide issues. In addition, individuals must also assume responsibility for their own well-being by adopting a healthier lifestyle, comprising an increase in physical activity and improvements in diet.

Although **predictive genetic testing** for type 2 diabetes is currently not recommended, it is of potential future interest for a **personalised preventive medicine programme**. Screening subjects at a perceived high risk for developing type 2 diabetes may be important in terms of individual health and public health policy, but a consensus is needed on the criteria for initiating the screening. Because of the long asymptomatic period of type 2 diabetes, reasonable **screening methods, new diagnostic tools and improved and new markers** need to be developed to allow of an early diagnosis. New **biomarkers** for insulin resistance, a hallmark of type 2 diabetes and the pre-diabetic state, are being developed and include adiponectin – currently the best predictive marker for type 2 diabetes and myocardial infarction – vaspin and proinsulin. Inflammation markers such as TNF α , IL-6 and CRP are increased in adipose individuals and have also been found to be predictive for type 2 diabetes and its late vascular complications. Therefore, the development and validation of such biomarkers may also contribute to a **personalised preventive medicine programme** and improve **diabetes screening**.

Diabetes Complications and Need for Tight Glycaemic Control

Diabetes mellitus is associated with the development of **specific long-term organ damage** (diabetes complications) including retinopathy with potential blindness, nephropathy with a risk of progression to kidney failure, neuropathy with a risk of foot ulcers, amputation and Charcot joints as well as autonomic dysfunction such as sexual impairment. Patients with diabetes are at a particularly high risk for cardiovascular (e.g. myocardial infarction), cerebrovascular (e.g. stroke) and peripheral artery disease. The most common cause of death in European adults with diabetes is coronary artery disease. As several studies have demonstrated, they have a risk which is two to three times higher than that among people without diabetes. In addition, people with diabetes experience greater disability and poorer quality of life than the general population.

The need for **tight glycaemic control** has been demonstrated in the UK Prospective Diabetes Study (UKPDS) and the Kumamoto Study in patients with type 2 diabetes. A subsequent analysis of the UKPDS cohort showed an approximate 14% reduction in myocardial infarction for every 1% reduction in HbA_{1c}. However, many patients do not achieve good blood sugar control with current therapies.

Diabetes Therapy

A **personalised treatment** approach for patients with diabetes is necessary for several reasons. First of all, diabetes is a highly complex disease caused by the interplay between genetic, physiological and environmental factors that vary from individual to individual. Secondly, the profile of patients with diabetes has evolved to include people of all ages and socioeconomic backgrounds, with different medical histories and health behaviours. Thirdly, diabetes often occurs concurrently with other medical conditions, especially in certain groups, such as the elderly. While the treatment goals for all patients with diabetes are the same – to stabilize and maintain healthy blood glucose levels to prevent serious complications – the treatment plan used to achieve those goals will vary in each individual case.

The first step in diabetes therapy includes modification of diet, regular exercise, and usually weight loss. These **lifestyle measures** have been shown to effectively improve blood sugar control but, unfortunately, are difficult to maintain. The large majority of patients with type 2 diabetes will need additional medication during the course of their diabetes.

Today's physicians are confronted with a wide variety of oral, injectable and very recently also inhaled medication available for the treatment of type 2 diabetes. The **main classes of**

antidiabetic medicinal products are different in their modes of action, safety profiles and tolerability. Despite the various medicinal products available for the treatment of type 2 diabetes, many patients do not achieve good control of their blood glucose, reflecting the **limitations of current pharmacotherapy**. Therefore, new effective antidiabetic medicinal products and treatment strategies are needed. Overall, a **paradigm** shift in diabetes treatment towards the development of drugs for beta-cell preservation and/or regeneration is expected. In addition, genetic variants such as TCF7L2, S447S, Arg972 or Pro12Ala have been implicated in increased or reduced response to certain antidiabetic agents or the susceptibility to certain adverse effects. Therefore, genetic testing may be of potential future interest for **predicting treatment response and/or adverse reactions**.

Conclusions and Outlook

Several intrinsic and extrinsic risk factors for the development of type 2 diabetes have been identified. Beside other factors, **genetic variations** have been associated with the disease. Because of the long asymptomatic period of type 2 diabetes, reasonable **screening methods, new diagnostic tools and improved and new markers** are required to allow an early diagnosis.

Despite the various drugs available for treatment of type 2 diabetes, many patients do not achieve good blood sugar control, reflecting the **limitations of current pharmacotherapy**. Therefore, new and more effective antidiabetic medicinal products are needed. Additionally, more emphasis may have to be placed on a **personalised therapy** than the currently more frequently practised 'one fits all' treatment approach.

Due to the steadily increasing prevalence of obesity and particularly metabolic syndrome, we are facing a worldwide epidemic of type 2 diabetes representing a major health issue and socio-economic burden. Public health strategies are needed to address these population-wide issues. This should not only include the person's genetic disposition and genotypical background, but also his/her lifestyle and diet. Furthermore, more knowledge is required about how the disease develops and works on the molecular level. This could lead to **new approaches in R&D of new personalised treatment concepts**.

VII. Workshop 6: Virology/Immunology

Human Immunodeficiency Virus-Infection

Viral diseases have a major impact on global health. The most relevant viral infection with respect to long-term consequences is the infection with **Human Immunodeficiency Virus (HIV)**, **due to its high prevalence** especially in young people and its rapid spread. Worldwide, more than 40 million people are presently living with HIV/AIDS, more than 700,000 of them in Europe. Therefore, **combating HIV/AIDS has been set as a priority goal by the United Nations** in 2000 and several national and international programmes (e.g. by WHO) have been initiated to accelerate therapeutic and epidemiological advances in this field.

Today's standard treatment of HIV-infection consists of a **combination of three antiviral agents**. Combining active ingredients is essential for the achievement of long-term antiviral efficacy by reducing the risk of development of viral resistance.

Dose selection during drug development is based on *average* values, e.g. *mean* plasma levels or efficacy (response rate) and tolerability in the *overall* study population. Thus, the recommended adult doses are usually uniform, with very few medicinal products differentiating between two doses taking into account the patient's bodyweight. This general approach, however, does not account for host factors involved in treatment response, such as human leukocyte antigen (HLA) variants or cytochrome P450 enzyme polymorphisms and, thus, it does not aim at the optimisation of therapy for the individual patient. This is confirmed by recent data showing that treatment response is achieved after 48 weeks by 73% of the Intent-to-treat population, whereas it is achieved in 95% of the As-treated population, i.e. in patients who do not withdraw prematurely from the studies⁸. Whereas the current practice of 'one dose for all' may lead to sub-optimal efficacy in some patients, it may as well result in safety concerns in others. The rate of discontinuations owing to adverse events in the aforementioned study, for example, is as high as 6%. Higher adverse event rates or more pronounced adverse events do not only have an impact on the quality of life but may also influence the morbidity and mortality of these patients.

There are several recent examples where pharmacogenetic factors in HIV therapy have been detected as predictive factors for side effects of antiretroviral drugs, such as the following:

⁸ Eron J Jr, Yeni P, Gathe J Jr, et al. The KLEAN study of fosamprenavir-ritonavir versus lopinavir-ritonavir, each in combination with abacavir-lamivudine, for initial treatment of HIV infection over 48 weeks: a randomised non-inferiority trial. *Lancet* 2006; 368: 476-82

- abacavir: Human Leukocyte Antigen (HLA) B5701 and – potentially life-threatening – hypersensitivity reactions,
- atazanavir: polymorphism of its metabolizing enzyme uridine diphosphate-glucuronosyl transferase (UGT) and hyperbilirubinaemia
- efavirenz: polymorphisms of its metabolising enzyme CYP2B6 and CNS toxicity, treatment response, and resistance
- nevirapine: polymorphisms of its metabolising enzyme CYP2C19 and CYP2B6 and hypersensitivity reactions and hepatotoxicity

The picture is becoming even more complicated when considering the complex drug-drug interaction profiles of many antivirals and the frequent need for additional concomitant medications in HIV-infected patients.

When considering the global disease burden with a preponderance of HIV/AIDS in the resource constraint settings it is crucial that relevant ethnic differences in these genetic factors, which have been uncovered over the last years, are accounted for. Therefore, pursuing the individualization of anti-HIV therapy is not just a matter of convenience, but maybe a matter of survival.

Hepatitis C Virus Infection

The disease burden of hepatitis infections is substantial – worldwide and in Europe as well. The most relevant entities are hepatitis B and C. **Hepatitis may become chronic and thereby lead to severe organ damage**, e.g. liver cirrhosis and liver carcinoma. In Europe, 3 to 5 million people are currently living with chronic hepatitis C.

Whereas the standard treatment of chronic Hepatitis B usually consists of one antiviral agent, chronic Hepatitis C is commonly treated with a combination of pegylated *interferon* plus *ribavirin*. Predictions of treatment response have been formulated for both types of hepatitis, such as viral genotype, baseline plasma viral load, patient age and gender. However, until now, only the viral genotype in **hepatitis C infection** plays a role for the selection of dose and the duration of antiviral therapy. Recently, results from the first studies personalising anti-HCV therapy based e.g. on baseline viral load or extent of initial drop in viral load have become available. Mathematical models have been applied in order to develop stopping rules in case of non-response in HCV-1 infected patients or in order to tailor treatment duration with interferons/ribavirin for avoiding unnecessary and potentially severe adverse reactions. Studies investigating HLA genotype and treatment response or the natural course

of the infection failed to show an association. Nevertheless, further optimization of dose and duration of anti-HCV treatment is a highly desirable goal, since side effects of therapy frequently occur, may be very severe and lead to incomplete adherence to therapy and, in consequence, unnecessary treatment failures.

Immunosuppressive Therapies in Transplantation

Subsequent to an organ transplantation, e.g. of a kidney, heart or liver, long-term immunosuppressive therapy is required for the prevention of organ rejection. Until now, only a handful of immunosuppressive agents is available. However, due to their inherent severe toxicities, a larger assortment of these agents is strongly needed.

Usually, the development of immunosuppressive therapies is long and risky, since heavy long-term non-human primate transplantation models are used and necessary to guarantee the efficacy and the safety of such medicinal products under similar transplantation conditions as in humans before successfully applying them to clinical trials. However, genomics technologies, such as new molecular understanding of patho-physiological processes in animals (e.g. toxicogenomics) and in humans (e.g. genomics biomarkers) have already started to transform profoundly and to accelerate many aspects of the drug discovery and development process, from target finding and validation to the selection of the right medicinal product for the right patient. The following examples demonstrate the usefulness of genomic technologies in immunosuppressive therapies/transplantation:

- Proof of Concept studies for new immunosuppressive therapies can be accelerated due to genomics technologies (e.g. **protein kinase C inhibitors**),
- Safety aspects can be clarified at an early stage to ensure selection of the right compounds and most efficient and safest combination therapies (e.g. **nephrotoxicity markers**),
- New biomarkers can be developed to predict chronic rejection episodes long before non-reversible histo-pathological damage occurs. This should allow early therapy adaptations to avoid organ failures due to such side-effects (e.g. **calcineurin inhibitors**). Examples include Kim1 and clusterin as markers of proximal tubular damage, and cystatin C, beta2-microglobuline and urinary protein for alteration of glomerular function.

However, some relevant issues, such as the detection of peripheral biomarkers for kidney damage, as well as development of validated bioassays, are still outstanding and further research is needed.

Influenza Vaccination

Awareness of the potential benefit of seasonal vaccination against influenza has steadily increased during the past decade and has been further boosted by the hypothetical threat of a new pandemic influenza virus evolving from the highly pathogenic avian influenza virus subtype H5N1 or from other influenza A virus subtypes. As a consequence, concepts have been developed during the past couple of years aimed at defining optimal vaccine formulations making it possible to combine two important rationales, i.e. (1) enhancing the immunogenicity of influenza virus antigens in order to achieve protective immunity after a maximum of two doses and (2) reducing the antigen content in order to optimally exploit existing manufacturing capacities.

In the course of these product developments, it became evident that, although they had existed already for decades, our knowledge of the efficacy and effectiveness of seasonal influenza vaccines is rather poor. Marketing authorisations for influenza vaccines are solely based on a number of immunogenicity parameters that must be met for each seasonal update and also for new influenza vaccines. However, correlation between serological variables measured and the level of protective immunity, in particular in children, the elderly and individuals with underlying acute and chronic diseases, is unsatisfactory. Moreover, modern split or sub-unit seasonal influenza vaccines as licensed in the EU appear to be only weakly immunogenic and, as single dose regimen, they are obviously only efficient in individuals who have acquired a sufficient level of residual immunity through previous vaccinations and/or regular contact with circulating human wild-type influenza viruses. It is presently unknown how to achieve protective immunity with these vaccines in individuals with insufficient or absent residual immunity. However, epidemiological studies indicate that seasonal influenza vaccines do indeed have a positive benefit/risk ratio for the population for which these vaccines are officially recommended. Nevertheless, besides the lack of randomised controlled clinical trials to clarify the above mentioned open issues evidence from such epidemiological studies needs to be further improved. From that perspective, our knowledge about the clinical performance of influenza vaccines has to be improved, not only for new influenza vaccines but also for the established, i.e. licensed influenza vaccines. An appropriate clinical data base has to be established for each individual product or at least for product groups such as split or subunit influenza vaccines.

Conclusions and Outlook

Antiviral medications are available for the most relevant viral diseases. Presently, their application such as choosing the right substance (combination) or giving the right dose often depends on factors whose values representing the respective average of entire populations. For the individual patient, however, this may be sub-optimal and, thus, may affect recovery and survival. Therefore, an individualisation of the treatment is essential for substantial improvement of the medicinal product's therapeutic efficacy and safety. Beside parameters such as body weight, age and viral characteristics, ongoing and future developments will also focus on genotype-specific patient information, such as human leukocyte antigens or cytochrome P450 enzyme polymorphisms. On the one hand, this approach may finally facilitate the development of new medicinal products and, on the other hand, it may reduce side effects and the number of failures with existing products .

VIII. Workshop 7: Undesirable Effects/Toxicology

During drug development and prior to first use of a new pharmaceutical in human beings, a comprehensive preclinical testing programme has to be performed in order to ensure human safety. These non-clinical safety studies are conducted in tissue culture cells and laboratory animals (e.g. mouse, rat, dog, monkey). They include repeated dose toxicity studies to identify **target organ toxicity**, **reproductive toxicity studies**, **genotoxicity studies** and others. Although the majority of prospective active ingredients which cause severe and unacceptable toxicity are eliminated at these early stages of drug development, the predictive accuracy of extrapolating from preclinical species to humans is limited. This is one major cause of loss of potential medicinal products in the clinic where safety issues account for approximately 30% of drug development failures. Some toxic effects of active ingredients are even detected only after the medicinal product has been introduced on the market which, in severe cases, may result in the withdrawal of newly approved medicinal products from the market. Such **unexpected adverse drug reactions**, which do not involve the known pharmacological effects of the active ingredient and which occur randomly and usually dose-independently in patients, are commonly referred to as 'idiosyncratic' effects.

Idiosyncratic drug reactions (IDRs) are difficult to study and little is known with certainty about their mechanisms. IDRs include anaphylaxis, blood dyscrasias, hepatotoxicity, severe cutaneous reactions and other reactions. They are usually serious and can be fatal. It is assumed that not only the properties of the compound are responsible for the development of idiosyncratic reactions, but also predisposing factors among susceptible individuals. Associations have been suggested between a specific genotype, e.g. genetically

polymorphic metabolic enzymes and the risk of a specific IDR. There are other factors that have been found to be risk factors for specific IDRs, such as age, sex, weight, and disease state. It is clear that idiosyncratic drug reactions add a significant degree of uncertainty to the process of drug development. The ability to screen active substances to eliminate those that would cause such reactions would be a major advance. In order to accomplish this goal, a better understanding of the basic mechanisms of such reactions is essential.

New technologies like transcriptomics, proteomics and metabolomics, collectively referred to as 'omics' are meanwhile actively used in the pharmaceutical industry and have great potential to improve safety assessment during drug development. Several studies carried out recently have already demonstrated the benefits of applying '**omics-** platform technologies' towards drug safety evaluation, both for identifying mechanisms underlying toxicity, as well as improving species-to-species extrapolations. These methods are also promising for providing a means to assist early selection of most appropriate active ingredient candidates with respect to safety, efficacy, and drug metabolism profile.

It has been suggested that compounds with a high incidence of IDRs might induce specific and predictive gene expression patterns even in animals or patients who do not develop idiosyncratic reactions. For instance, **trovafloxacin**, a quinolone that has been removed from the market due to severe idiosyncratic liver toxicity not predictable from conventional preclinical studies, could be clearly distinguished from four other quinolones by using gene expression profiling in experiments with isolated human hepatocytes. While these data are still preliminary, they show the potential of the 'omic-' approaches for providing additional knowledge and give rise to the hope for using this technology to predict the probability of a compound for causing IDR in specific individuals. Ideally, gene expression changes that highly correlate with specific toxicity may be evaluated and confirmed at the protein level and ultimately be used to develop new biomarkers of toxicity which could facilitate safety evaluations in non-clinical as well as clinical studies.

Conclusions and Outlook

The investigation of undesirable effects and toxicology of pharmaceuticals is an important issue prior to and after their approval. Pre-clinical studies in these fields are conducted as a routine, but their significance for human use of the respective medicinal product is limited. Therefore, severe side or toxic effects are still a matter of serious concern. However, the prediction of undesirable and toxic effects is rapidly advancing due to the use of high-throughput and other novel molecular biological technologies. This will lead to significant progress in the testing strategies for idiosyncratic toxicity. On the other hand, an increasing

awareness of Regulatory Authorities with regard to the use and potential of these technologies in safety evaluation and how it might influence regulatory decision making in future is needed as well as desirable.

IX. Summary and Future Prospects

It has been shown that personalised medicine is an advancing field in research and development. Furthermore, personalised medicine has already been impacting on clinical practice for some indications such as cancer, psychiatry/CNS disorders or infectious diseases. A prerequisite for the personalisation of medicine is the identification of mechanisms and, in particular, the genes involved in disease and treatment. First biomarkers have been identified which can be associated with certain diseases. The association is a cumbersome work which requires careful validation once such associations are identified. The picture gets even more difficult when complex diseases caused or influenced by more than a single gene are to be analysed. Furthermore, genes encoding drug metabolising enzymes or transporters also have to be taken into account. The field is further complicated by differing genotypical backgrounds which can also impact on the success of a certain treatment.

The concept of personalised medicine has to compete with established strategies of drug development and disease treatment such as the 'one-fits-all' approach. This is a growing challenge, not only for pharmaceutical companies, but also for regulatory authorities and legislative bodies, among others. The stakeholders expect important innovations in the field of personalised medicine. Not only will these innovations have an impact on the health status of individuals; they will also affect health care systems and society as a whole.

In the light of this progress, the legal, regulatory and ethical framework has to be reviewed and adapted where appropriate to meet the challenges arising from personalised medicine. In particular, it is necessary to ensure that personalised medicine exhibits adequate quality, safety and efficacy, that patients get equal and fair access to the new forms of therapy and that patients' rights are not violated (protection of sensitive personal data, avoiding discrimination).

Only if these challenges can be met, can personalised medicine fulfil at least some of the enormous expectations with which it is associated today.