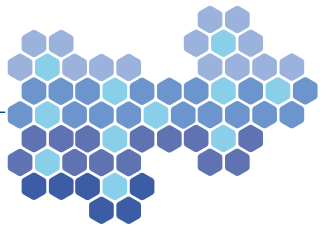

Delivering on the Promise of Personalised Medicine

By Guido Dallmann and Ralph Zahn at Biocrates Life Sciences AG

A far-reaching vision of personalised medicine is that it will become routine to know a patient's genetic background and metabolic status and, as a result, be able to treat disease with safer and more effective therapies.

Keywords

Personalised medicine
Pharmacogenetics
Diagnostics
Genomics
Transcriptomics
Proteomics
Metabolomics

About 2,400 years ago, Hippocrates evaluated factors such as a person's constitution, age and physique, as well as the time of year, to aid his decision-making when prescribing drugs. In 1902, Sir Archibald Garrod made the first connection between genetic inheritance and susceptibility to a disease. Since the complete sequencing of the human genome in 2003, personalised medicine has progressed rapidly – fertilised by the entire spectrum of molecular medicine, including proteome, metabolome and epigenome (1).

Modern 'non-personalised' medicine alone has made great progress in the diagnosis and treatment of a growing number of diseases. However, selecting an optimal therapy still follows a trial and error approach. The physician makes a diagnosis based on the patient's symptoms and then prescribes a drug and/or treatment. If a patient does not respond to the treatment or shows significant side effects, the dosage is adjusted or another drug is prescribed (if available). In some cases, the initial diagnosis has to be reconsidered. This is done until the right diagnosis and treatment plan are discovered – resulting in a time-consuming, frustrating and costly practice.

The discovery that differences in genes coding for drug-metabolising enzymes, drug transporters or drug targets cause the variability in drug response led to a reorientation. The science of pharmacogenetics then developed, with its focus on differences in drug response as a function of genetic differences among individual patients, and this knowledge about a patient's drug response represented an essential step towards optimising therapy.

It now seems obvious that an individual's genetic background in combination with age, nutrition, health status and environmental exposure are the key factors for a customised therapy.

Safer and More Effective Therapies

The most commonly cited promise of personalised medicine is that drugs and drug dosages will be safer and more effective. Here, the development of DNA-based diagnostic tests will help the physician to identify a disease, select the right treatment and determine the right dosage. In the context of drug safety, these tests will help to identify patients who will benefit from certain drugs and those who risk developing serious side effects. The example of Merck's rofecoxib (Vioxx®) illustrates the crucial need for improving drug safety. In 1999, rofecoxib was approved by the FDA, and in 2004 it was withdrawn from the market on the basis of a possible link with an elevated risk of suffering a heart attack.

A far-reaching vision of personalised medicine is that it will become routine to know a patient's genetic background and, as a result, be able to effectively treat diseases – as well as identify disease risk and prevent disease by, for example, changes in lifestyle or early intervention.

For the pharmaceutical industry, knowledge about the human genome is a valuable tool because drug development is a costly and lengthy process. Understanding the genetic basis of a disease and its progression will help to identify biochemical pathways that can be targeted with new and more potent drugs. In the drug development process, genomic data can help to save resources and time by focusing on those drug candidates most likely to be safe and effective.

Where Do We Stand Now?

Today, thousands of patients with melanoma, breast or lung cancer, and leukaemia have already benefited from personalised medicine. They are routinely offered a molecular diagnostic investigation, enabling treatment with a selected tailored medicine (2).

Optimal Therapy versus Trial-and-Error Prescribing

In many cases, patients do not benefit from the first drug they are offered by the doctor. Instead, they lose valuable treatment time by trying various drugs on a random basis. For example, 38 per cent of depression patients will not respond

to initial treatment. Even if a patient is prescribed an effective drug, there may be better ones on the market.

The antibody drug Herceptin® can be regarded as a sort of pioneer in personalised medicine. It is effective for about 30 per cent of women with breast cancer for which standard therapy is not effective. The responding women are characterised by over-expression of human epidermal growth factor receptor 2 (HER2). Herceptin® binds to HER2 on the surface of cancer cells and tumour growth is inhibited when used in combination with chemotherapy. The HER2 molecular diagnostic test can thus be used to identify patients who will benefit from this rather expensive antibody drug treatment.

Shift of Emphasis from Reaction to Prevention

Molecular markers that signal the risk or presence of a disease before symptoms appear offer the opportunity to focus on prevention and early intervention, rather than reaction at a more advanced stage of disease. For example, women with BRCA1 or BRCA2 gene variations have a 36 to 85 per cent lifetime chance of developing breast cancer, compared with a 13 per cent chance among the general female population. The BRCA1 and BRCA2 genetic tests can guide preventative measures such as increased frequency of mammograms, prophylactic surgery and chemoprevention.

Safer Drugs by Avoiding Adverse Reactions

About five per cent of all drugs are associated with adverse drug reactions (ADRs). Many ADRs are the result of gene variations of the cytochrome P450 (CYP450) enzymes, or related drug-metabolising enzymes. ADRs are generally the result of drugs being metabolised either faster or slower compared with the general population, resulting in either rapid drug elimination or overdose toxicity, respectively. To prevent this, the FDA has approved various assays detecting variations in genes. Recently, the FDA recommended genotyping for all patients before administration of the drug warfarin, used for blood clot prevention; suboptimal dosage can lead to excessive bleeding or further blood clots.

Revival of Failed Drugs

If a drug or drug candidate fails, it can be revived by limiting its use to genetically-defined patient populations. This can save on huge development costs by converting the 'failed drug' into a marketable product. For example, the lung cancer drug gefitinib (Iressa®, AstraZeneca) did not demonstrate a survival advantage in a general population of patients in clinical trials, and was withdrawn from the market after initially being granted 'accelerated approval'. Using pharmacogenetics, it was possible to demonstrate that about 10 per cent of patients with epidermal growth factor mutations benefited from the drug, which subsequently received approval for line treatment in the UK.

Obviously, compliance with treatment leads to favourable health outcomes and lower overall health costs, with the proviso that personalised therapies are more effective or present fewer side effects. Incorporating personalised medicine into the health system may help to resolve trial-and-error dosing, late diagnoses, hospitalisations due to adverse drug reactions and reactive treatments. Not to be underestimated is the fact that personalised medicine can also improve quality of life; for example, a simple blood test is more comfortable for the patient than an invasive and time-consuming biopsy.

The Role of Metabolomic Biomarkers

The 'omics' technologies – genomics, transcriptomics, proteomics and metabolomics – represent approaches to identifying multiparametric biomarkers characteristic of a particular disease within a set of genes, mRNA, proteins and metabolites (1,3). Metabolomics is the latest omics technology and is the closest to expressing the phenotype of a given organism (4). It is the non-biased identification and quantification of metabolites in a biological system. The ultimate goal is the study of chemical processes and pathways involving metabolites – or specifically, the systematic study of the unique chemical fingerprints that specific cellular processes leave behind. The metabolome represents the collection of all metabolites in a biological cell, tissue, organ or organism that are the end-products of cellular processes. The common methods used in metabolomics are mass spectrometry (MS) and nuclear magnetic resonance (NMR) spectroscopy (5). A recent approach involves the combination of MS and NMR data analysis, with the goal of identifying unknown metabolites and their assignment within the Human Metabolome Database (6).

Metabolomics is a novel area, enabling the molecular characterisation of various phenotypes and identification of personal metabolic features, closing the gap between phenotype and the other omics technologies. In this context, the combination of metabolomics and genomics provides, for example, new insights into gender-specific differences in serum metabolite concentration and their underlying genetic determination (7). Metabolomic analysis has two major potential applications: first, the early diagnosis and characterisation of disease phenotypes; and second, the prediction of drug effectiveness and/or toxicity – an approach called pharmaco-metabolomics.

Today, MS-based 'targeted' metabolomics is commonly used in the diagnosis of inborn errors of newborns (8). Infants are

screened shortly after birth for a list of disorders that are treatable, but are difficult or impossible to detect clinically. Examples include phenylketonuria, congenital hypothyroidism and congenital adrenal hyperplasia (CAH). Whole blood samples are collected from the infant's heel on specially designed filter paper, and then tested by various technologies – with most parameters being analysed by tandem mass spectrometry (MS/MS). Screening programmes are often run by national governing bodies, with the goal of screening all infants born within the jurisdiction.

Apart from 'newborn screening', no biomarkers related to prognosis or diagnosis of a disease or drug toxicity/efficacy discovered through metabolomics are used routinely in clinical diagnostics at the present time. For this purpose, biomarkers must fulfil certain utility criteria such as:

- Can the clinician measure the biomarkers?
- Do the biomarkers add new information?
- Do the biomarkers help the clinician to improve patient treatment (9)?

However, there is no reason to believe that metabolic biomarkers cannot be used for clinical applications such as early detection of subclinical disease, risk stratification of patients, selection of the right treatment and monitoring the response to therapy. Indeed, at a scientific level, there are various examples of how metabolic biomarkers provide novel insights into the pathophysiology of disease and disease progression. For example, Wang and colleagues examined the relationship between asymmetric dimethylarginine (ADMA), symmetric dimethylarginine (SDMA), arginine methylation index and coronary artery disease phenotypes (10).

Only a Matter of Time

The bottleneck for the use of metabolomics in routine clinical practice is the availability of sampling procedures and analytical methods that allow accurate, high-throughput measurements with prompt turnaround time and low costs. Although metabolites such as glucose, cholesterol or creatinine are measured routinely, the MS-based technology that is needed for metabolomics is still not widely available. But, it will be only a matter of time until this new technology, capable of the simultaneous quantification of a large number of metabolites, complements or even replaces current single-parameter diagnostic assays. Particularly targeted metabolomics has great potential for use in modern clinical diagnostics, since the resulting multi-parametric data are absolutely quantitative – thus enabling highly accurate, diagnostic analysis at an advanced medical level.

Dr Guido Dallmann is a trained analytical chemist, and graduated in Biochemistry at the University of Wuppertal (Germany). He is experienced in developing MS-based bioanalytical methods, with a background in targeted metabolomics. He joined Biocrates 2009 and is currently Group Leader for Biomarker Development, and is responsible for research projects to identify and validate metabolomic biomarker panels in selected diagnostic and medical areas.
Email: guido.dallmann@biocrates.com

Ralph Zahn joined Biocrates Life Sciences AG (Innsbruck, Austria) in 2010 as Chief Technology Officer with responsibility for development of the new product pipeline, and affiliated technical and scientific assignments. He holds a PhD in natural science and has a wealth of experience in the field of biotechnology. During his career, he has worked as Managing Director of BioSafety GmbH and founder and Chief Executive officer at allprion AG.
Email: ralph.zahn@biocrates.com

References

1. Meyer JM and Ginsburg GS, The path to personalized medicine, *Curr Opin Chem Biol* 6: pp434-438, 2002
2. The Case for Personalized Medicine, 3rd edition, Personalized Medicine Coalition
3. Sauer U, Heinemann M and Zamboni N, Genetics: Getting closer to the whole picture *Science*: 316, pp550-551, 2007
4. Nicholson JK and Lindon JC, Systems biology: Metabonomics, *Nature* 455: pp1,054-1,056, 2008
5. Baraldi E, Carraro S, Giordano G *et al*, Metabolomics: moving towards personalized medicine, *Italian Journal of Pediatrics* 35: p30, 2009
6. Pan Z and Raftery D, Comparing and combining NMR spectroscopy and mass spectrometry in metabolomics, *Anal Bioanal Chem* 387: pp525-527, 2007
7. Mittelstrass K, Ried JS, Yu Z *et al*, Discovery of sexual dimorphisms in metabolomic and genetic biomarkers, *PLoS Genet* 7(8), available at www.plosgenetics.org/article/info%3Adoi%2F10.1371%2Fjournal.pgen.1002215
8. Liebl B, Nennstiel-Ratzel U, Roscher A and von Kries R, Data required for the evaluation of newborn screening programs, *Eur J Pediatr* 162: Suppl 1, S57-S61, 2003
9. Mamas M, Dunn WB, Neyses L and Goodacre R, The role of metabolites and metabolomics in clinically applicable biomarkers of disease, *Arch Toxicol* 85(1): pp5-17, 2011
10. Wang Z, Tang WH, Cho L and Brennan D, Targeted metabolomic evaluation of arginine methylation and cardiovascular risks: potential mechanisms beyond nitric oxide synthase inhibition, *Arterioscler Thromb Vasc Biol* 29(9): pp1,383-1,391, 2009