Interview with Andreas Ruppert, Head of GSK's Genetics Research Centre (GRC) in Munich

"Up to 600,000 SNPs per week"

The Genetics Research Centre (GRC) in Munich is an industry-driven institute whose customers are mainly from academia. *Lab Times* reporter Karin Hollricher met its Head, Andreas Ruppert, at Analytica 2008 – and was inquisitive.

Lab Times: *What kind of scientific service does the GRC offer?*

Andreas Ruppert: The GRC helps the customer or the collaborator, which is in most cases the more adequate term, to perform high throughput genotyping studies in an industrial setting.

You're doing whole genome scans?

Ruppert: No, currently we do not perform genome-wide associations studies. Those studies typically start with an oligo array format. This allows for a completely hypothesis-free approach. For whole genome scans you test less numbers of DNA samples from patients and controls because it is so expensive. After having revealed first associations between SNPs and a disease or any other phenotype you try to further define and validate positive SNPs and you search additional SNPs that were not covered by the platform you've chosen for the initial genome scans.

"One has to carefully differentiate between genetic testing and diagnostic testing. In the public press these terms and the ideas behind them are often mixed up. What we do here at the GRC is genetic testing."

So what is your speciality?

Ruppert: Like in typical candidate gene approaches, we analyse SNPs in defined chromosomal regions or even within or near certain genes the customers have previously identified as being associated, for example, with a disease or to drug response. So our customers typically know which regions of the chromosomes or even which genes might be involved. We are able to perform high throughput genotyping, which is still required at this stage of a study to further define the genes to do SNP or gene validation studies.

Who is your typical customer?

Ruppert: Our customers are mainly from academia. But we're also genotyping for GSK researchers from the USA and UK. We are kind of proud of that because scientists in the USA do not often retrieve additional services from European companies and laboratories. Since we moved in early 2005 to a building of the Ludwig-Maximilians-Universität (LMU) in the centre of Munich we have had a close collaboration with the molecular genetic workgroups within the Clinic of Psychiatry.

But you are not limited to problems and questions of psychiatry or even medicine. Can you also do genotyping on plants or animals?

Ruppert: We can do all types of research where genotyping is involved.

Enthusiastic about the GRC: The institute's Head, Andreas Ruppert.

Do you also offer the interpretation of your data?

Ruppert: No, absolutely not. We only have and will work with anonymous samples. We do not know from whom the DNA samples we are working with are derived and have no access to individual data or patient records.

What would be a brief description of your technology?

Ruppert: We're using a mass spectrometric based genotyping system to analyse DNA from patients and from control individuals that is provided by the customer. It involves the primer extension of a SNP specific oligonucleotide by one nucleotide using the DNA samples as templates. This added nucleotide can be identified by mass spectrometry. It gives us the information about which SNP allele is present in the individual DNA sample. We can analyse up to 600,000 SNPs per week. Typically we perform about 1,000 to 3,000 DNA samples which are tested against 100 to 500 SNPs.

"There is a limited number of labs we compete with. Our equipment is second to not many labs in the world."

Why do you apply this method?

Ruppert: The technology was originally developed by the company Sequenom. It is much more precise and accurate than hybridisation based analyses due to the fact that we are able to analyse DNA fragments directly. There is no reporter like light emission necessary to identify the added SNP-specific nucleotide. We get less false positive signals compared to other technologies.

For genotyping defined regions you need more SNPs than those provided by whole genome scan platforms. Do you also develop new SNPs for particular genes and DNA regions?

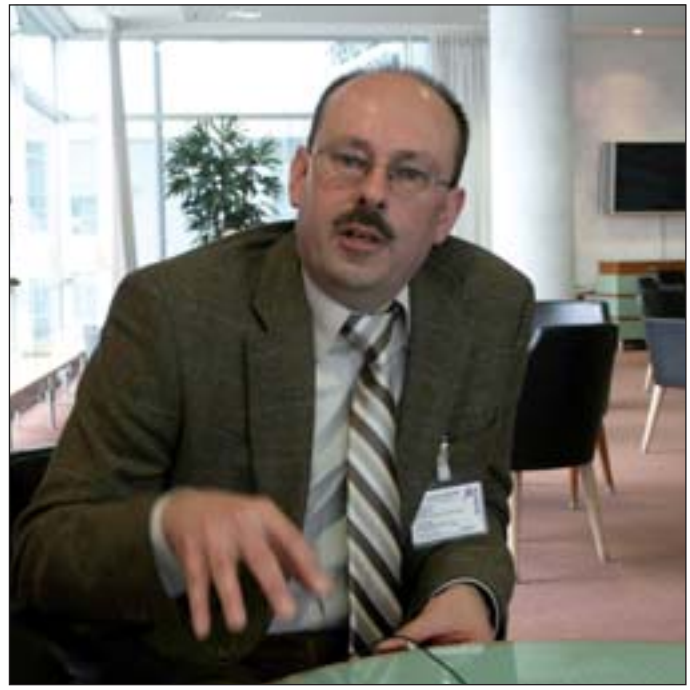
Ruppert: Indeed, we do use other SNPs in addition to the SNPs provided on whole genome scan platforms which cover some 500,000 to 1 million SNPs. Since at least three million SNPs are present in the genome you'll easily miss the potential causative SNP which you're interested in. Our speciality is analysing more SNPs in a closer distance to a certain locus than provided by SNP array formats. By doing that we can identify SNPs that are associated with or even cause a disease or a certain drug response.

For example?

Ruppert: The HIV drug Abacavir, developed by GlaxoSmithKline, can provoke a severe side effect, a potentially life-threatening hypersensitivity reaction within 3-8% of the patients. This side effect occurs only in those patients that carry the HLA-B*5701 genotype. This genotype can be identified by a SNP test. In clinical tests it could be shown that negative tested patients did not show any case of the hypersensitive reaction. As a result doctors are recommended to screen patients prior to prescribing the drug. The GRC was involved in an early stage of the genetic studies.

But the GRC doesn't develop diagnostic tests, does it?

Ruppert: No, we would not do diagnostic testing. One has to carefully differentiate between genetic testing and diagnostic testing. In the public press these terms and the ideas behind them are often mixed up. Genetic testing is a basic research tool to provide knowledge about genetic markers which helps to identify causative variations. Those markers are not validated at that stage. Whereas a diagnostic test is established and validated to provide information about certain SNPs in a patient which can be used by a physician for selecting an adequate therapy.



Photos (2): Hollricher

With respect to science, isn't it boring to work on numbers alone and never to know the result of your work?

Ruppert: Well, you know, a SNP genotype alone never tells the whole story. One needs to identify the function of the gene which shows association as revealed by SNP analysis. In the GRC we only do a small part of the entire chain from first description of a disease until identification of factors causing the disease. The major part of my work is to make contacts and to help to adopt scientific questions to the technology. To answer your question, no, my work is not boring. Our service is more than running a mass spectrometer, it's running an entire process from acquiring the samples, setting up the enzymatic reactions – the key of the process – and to bring the analyte in a format and purity under constant conditions to do high throughput studies. Systems like ours are too expensive for academic work groups but especially useful for many basic research approaches. There is a limited number of labs in Europe we compete with, for example labs at the Sanger Centre or at the Karolinska Institute to name just two. Our equipment is second to not many labs in the world. INTERVIEW: KARIN HOLLRICHER