Conference Scene

Four decades of modern pharmacogenomics: from promise to clinical utility

World PGX Summit 2011
Boston, USA, 26–27 April 2011

The World PGX Summit was held in Boston and preceded by a 1-day workshop. The conference aimed at assessing the current 'state-of-the art' in advanced molecular profiling strategies for increased drug development success. The topics varied from regulatory policies, pharmaceutical case examples and vendor presentations on innovative technologies. The subject is obviously closely related to personalized medicine and it was interesting to hear the perspectives from healthcare providers and subscribers. It became clear during the meeting that we are on the verge of important changes in how pharmaceutical research and development operates but also how increased costs and high unmet medical needs require new models in which pharmacogenomics can play an important role.

Pharmacogenomics studies the variations of DNA and RNA characteristics as related to drug response [101]. This term is often interchanged with pharmacogenetics, which limits studies to DNA. Although at this conference, despite the title, the majority of presentations were on DNA variation. These are interesting times after a decade of promises from sequencing the complete human genome. Technological advancements seem to result in sheer unlimited possibilities to study human genetic variation. Pharmaceutical research and development (R&D) and healthcare are in constant flux and the demand for personalized healthcare puts pharmacogenomics back under the spotlight. This conference was certainly not comprehensive and didn't answer all the questions, but the presentations and discussions allowed gaining a good insight in the current thinking and state-of-the art in the field of pharmacogenomics.

Pharmacogenomics moving forward: four decades

The first presentation was given by Peter Groenen (MSD, Netherlands), setting the stage by trying to make an objective assessment of the current achievements of pharmacogenomics. The main question the pharmacogenomics community has to ask itself is: 'are we beyond the hype?'. A paper by Hudson *et al.*, from 2006 described how pharmacogenetics testing will change the landscape of neuropsychiatric disorders, in particular [1]. By 2011 we would have around 4000 tests particularly in the challenging area. Though it is recognized that the mining of PubMed, patent and

genetic association databases was not comprehensive, it is accurate enough to conclude a totally different reality 5 years later. Pharmacogenomics has made progress, though more slowly than originally anticipated and we still have to overcome a number of scientific, and not in the least regulatory and societal hurdles.

Lawrence Lesko (US FDA, USA) presented the regulatory perspective and expressed his belief that we are living in interesting times where pharmacogenomics is starting to gain momentum both in pharmaceutical R&D as well as in clinical utility. There is a clear recognition that treated patient populations often display a wide spectrum of responses and sometimes also adverse events (AEs) or serious adverse events (SAEs). Preclinical models are often inadequate and safety assessments are empirical. At the same time the costs of technologies such as genome-wide association studies and genome-wide sequencing (next-generation sequencing) have rapidly decreased. In this perspective, he stated that in the general investigational new drug and new drug application reviews the US FDA will pay closer attention to proper research being conducted for understanding heterogeneity in patient populations intended to treat. Looking at the 21 new drug application/biologic license application approvals from January–September 2010, only 29% did not list a link to genetics or genomics. The FDA has obtained a good insight in the relation between drugs and genomic studies in the Voluntary Omics Data Submission (VXDS) process since 2002 where about 75 VXDS or Voluntary Genomics Data Submission

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(VGDS) have been reviewed. Of note, is also the constant review of drug labeling and the necessary changes based on new pharmacogenomics findings. Lesko indicated that the FDA can request a postmarket review (PMR) in which analysis of DNA and/or RNA samples is required. Altogether the rapidly changing landscape has urged the FDA (but also European Medicines Agency and the Japanese equivalent, the Pharmaceuticals and Medical Devices Agency [PMDA]) to draft a number of guidelines around pharmacogenomics and more recently, related documents around personalized medicine and companion diagnostics.

This optimistic, but not completely contrasting view on the progress and acceptance of pharmacogenomics is interesting and remained a theme throughout the conference. Amelia Warner (Merck&Co, USA) subsequently demonstrated that within Merck only 5% of the current studies had a prospective hypothesis to be tested, whereas 25% are retrospective with the majority of the studies in oncology and CNS research. Merck is now evaluating potential hurdles in their pipeline more systematically by addressing variability in genes causing possible PK and/or PD variability. The so-called PGx-backgrounder, a living document that is initiated around start of lead optimization, forms the basis of capturing all the vital information around genes, disease and drug response. It aims to capture all potential issues early, in order to identify genetic associations with drug response and/or (S)AEs rapidly to meet the challenging timelines in drug development. However, the question remains how much impact all of these internal studies can have. A number of success stories exist [2], however, on the second day of the conference Bryan Dechairo (Medco Research Institute, USA) made some provoking comments on the success rate of internal studies. He presented a very interesting series of slides on the Medco initiatives in pharmacogenomics and more in particular, personalized medicine. Medco is a pharmacy benefit manager processing around 0.5 billion prescriptions in 2010. He made two very interesting statements. First, we will not fulfill the promise of personalized medicine if we put the drug

first. We have to strive for improved diagnosis before we start prescribing the very average efficacy drugs, so diagnostics first. Second, because of the vast amount of longitudinal data they have, pharmacy benefit managers may be in an excellent position to overcome some of the problems of our current genetic association approaches: limited sample size and phenotypic data. Peter Groenen in the beginning of the conference already stressed the fact that current methodology is limiting our successes and sample size is one way that we can overcome our problems but more accurate phenotypic assessments maybe an equally large bottleneck.

Pharmacogenomics & innovative approaches

How do we balance these apparent challenges between drug development and clinical utility of diagnostic tests for efficacy and safety? Does technology provide the means to make the leap from hype to reality? Certainly, a number of presentations suggest that this will make a difference. The rapidly evolving next-generation sequencing technologies did not go unnoticed by the community. Joyce Peng, representing the world largest sequencing facility, Beijing Genomics Institute (BGI, USA), gave a nice overview of the current capacity and consequences on how we will approach pharmacogenomics in the future. Sequenom's MassArray technology positions itself somewhat in the medium throughput niche but provides significantly better quality and detection sensitivity. Charles Cantor (Sequenom Inc., USA) gave some key examples, specifically in the absorption, distribution, metabolism and excretion (ADME) testing area where dedicated panels can be used for a broader set of genetic polymorphisms. Certainly, increased scale and reduced costs can make a huge difference. But in the discussions during the conference it became clear that there is still a divide. Next-generation sequencing still hasn't matured and despite Moore's law, data storage and analysis will remain a bottle neck. A theme revisited from the first day and addressed in several presentations: the role of the regulators and most importantly, the payers. Eric Lai (Gen Probe, USA [formerly GSK]) once presented

an interesting analogy to the history of mobile phone development. It took over 30 years before cell phones became completely embedded in our society despite the available technology [102].

Clinical utility: from exploration to implementation

Obviously, the conference attendees were looking forward to presentations of case examples, especially by probably one of the earliest proponents of a very proactive attitude to the use of PGx in clinical development, Allen D Roses (Cabernet Pharmaceuticals [formerly GSK], USA). Roses gave a very interesting case example on the genetic variability in the *TOMM40* gene and the potential of developing a predictive diagnostic test for the age at onset of late onset of Alzheimer's disease (LOAD). The *TOMM40* gene is adjacent to *APOE* and in strong linkage disequilibrium.

Roses *et al.* found a variable length poly-T tract in the intron between exon 6 and 7 appears to be tightly correlating with the LOAD age of onset [3]. A clinical trial design has been proposed for a long-term prospective trial, and recently an agreement between Zinfandel Inc. (NC, USA) and Takeda (Osaka, Japan) was announced to develop a diagnostic test. While neurological and psychiatric disorders seem to be in highest need for improved diagnostics and predictive markers, things are generally more complicated than this elegant example. The quest for genes explaining variable response to risperidone presented by Nadine Cohen (Johnson&Johnson, USA) turned out to be quite frustrating. Despite numerous attempts and the development of a dedicated SNP array, Cohen *et al.* were not able to replicate earlier findings and were left with a relatively large number of samples that were genotyped but did not deliver a conclusive predictive marker for antipsychotic response. A discussion with the audience dismissed the use of clinical outcome such as the Positive and Negative Symptoms Score for association studies. On the morning of the second day, Abdel Halim (Daiichi Sankyo, USA) presented a nice overview of implementing a decision marker in the R&D workflow. Not

only do regulatory hurdles appear, but also the internal stakeholders are confronted with many changes and uncertainty in lack of clear regulatory guidance for companion diagnostics.

Conclusion

After 2 days of state-of-the-art overviews one is still left with the question of if we have made significant progress or got stuck with a few examples? There are sufficient signs that things are changing, not in the least because of the technological advancements. The examples remain few but there is common understanding that genetic factors play an important role in variable response and (S)AEs. Whatever the choice of technology two main bottlenecks remain: statistical/methodological limitations and clinical uptake. The latter influenced by regulations but also reimbursement policies. The sample-size limitations can at least be partially overcome, as was shown by Arthur Holden (SAE consortium) where different industrial partners put their samples together and explore in a pre-competitive fashion. The pharmaceutical industry is facing many challenges and a new working model to advance the benefits of PGx much quicker is an open innovation model. While the SAE consortium is focused in its goals, Michael Burczynski's (Hoffmann-La Roche, USA) message is clear: collaborate in each step whenever possible. This makes maximal use of the limited internal resources and uses the external academic knowledge of, for example, contracted postdoctoral assistants.

Finally, Amir Snapir (Orion Pharmaceuticals, Finland) and Lei Li (Pfizer, USA) addressed two vital components, sampling and quality control for sample processing. The first is a process for which, looking at the surveys by the Industry Pharmacogenomics Working Group [4], still many companies have variable and suboptimal processes in place. While DNA sampling is hampered by factors such as ethical committees, RNA strategies are not fully utilized. Sampling and proper (robust) procedures for processing are yet another factor that may explain the many examples of nonreplication of genetic response markers.

The future looks bright for pharmacogenomics, at least to some of the presenters. History however, warns of becoming over-optimistic. Most of the predictions have come true, but many years later than predicted. The increased attention by pharmaceutical companies to change their business model and take clinical variability as the starting point and not as the curse, will drive the evolution of pharmacogenomics.

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■ Websites

- 101 International Conference on Harmonization. Definitions for genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data and sample coding categories *ICH-E-15*, (2004) www.ich.org

- 102 Presentation by Eric Lai and other speakers (currently Gen Probe, formerly GSK) at the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology meeting, 18 March 2008 www.fda.gov/ohrms/dockets/ac/08/slides/2008-4351s1-01-GuestSpeakers-corepresentation.ppt