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editorial

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Pharmacogenetics—pivotal to the future of the biopharmaceutical industry

The inaugural London Genetics Pharmacogenetic Conference, 'Harnessing Genetic Knowledge To Improve Clinical Development and Patient Care', was held last autumn in the UK. With speakers from the biopharmaceutical industry, academia, regulators and health care organizations, the place of pharmacogenetics in the future of drug development was debated. Pharmacogenetics is the study of how our genetic make-up affects our response to drugs and leads to the area of stratified (or personalized) medicine, in which drugs are given to those who are expected to be responders or not suffer from side-effects. The discipline is all about finding the right drug for the right patient at the right dose.

Challenges to the industry

Apart from the challenges of increasing innovation and productivity, at the same time as increasing drug safety, the fourth hurdle of cost-effectiveness is becoming increasingly high profile for the industry as a result of countries (particularly the USA) focusing on healthcare budgets. Pharmacogenetics is seen as one of the leading emerging translational sciences to help meet these challenges [1], which no company involved in drug discovery and clinical development can afford to ignore. Although it is clear that genetics and pharmacogenetics have much value to add in the areas of finding drug targets, increasing specificity, reducing side-effects and improving patient selection, the question appears to be how we use the myriad of genetic and pharmacogenetic data that is becoming available to us.

Pharmacogenetics progress so far

Stratified medicine has arrived to a certain extent, and oncology is the poster child. In this area, the advent of pre-treatment genetic testing to identify responders and non-responders drives the prescription of both Herceptin and Erbitux. There has also been progress in the HIV area, with genetic testing to identify those most at risk of severe skin hypersensitivity reactions to Ziagen. Results from clinical studies also support the importance of genetic variation in our response to drugs such as Plavix and warfarin. These examples in fact encapsulate some of the potential of pharmacogenetics—the ability to select responder populations,

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BOX 1

Key messages from the London Genetics Pharmacogenetic Conference

- The biopharmaceutical industry faces an unprecedented set of challenges
- Genetics and pharmacogenetics offer great potential in meeting these
- Use in the clinical trial process, not just diagnostics and genetic tests
- Can lead to more effective, safer drugs and increased research productivity
- Genetics and pharmacogenetics are an important part of the puzzle
- Their exact role and place in research needs to be clarified
- Early collaboration between academia, industry, regulators and payers needed
- The need to show cost-effectiveness is hugely important

the potential ability to exclude those most at risk of side-effects and the ability to tailor dosing to individuals. However, most of this evidence was generated from studies conducted after drug approval. The challenge ahead is to use this technology early in the clinical trial process to increase effectiveness and efficiency and to deliver more effective and safer drugs, with increased chance of gaining regulatory approval and, importantly, reimbursement. Evidence of the increasing big company interest in this area has come in the acquisition by Qiagen of the UK personalized medicine company DxS, just as the London Genetics conference started. The LGL conference highlighted many of the pertinent issues in pharmacogenetics at the moment, which are discussed below (Box 1).

Cost-effectiveness

In a provocative after-dinner speech at the conference, Steve Arlington of PriceWaterhouse Coopers discussed the need for prevention and cure to be the new industry focus for healthcare costs to be kept at a reasonable level. Saying that the industry is 'not incentivized' to provide prevention and cure because long-term treatments are reimbursable, he suggested that the payers 'don't want (insurance) claims' and the industry will now be forced to 'prove drugs work'. We can expect 'high costs' for 'specialized drugs that prevent and cure' and the need to sell 'pills by outcome'. What part can pharmacogenetics play in this area? The message from the conference was that with the potential to select responsive patient populations, as well as to exclude those whose genetic make-up means that they are most susceptible to side-effects, pharmacogenetics has a key part to play.

Change the way clinical trials are done?

Many commentators noted that with the regulators interested in pharmacogenetics (Table 1), as well as the industry, the need for collaboration is great. Looking at how the industry does clinical trials now, we use Phase III populations that consist of non-responders to the drug, partial responders and responders. In a 'utopian' industry, Phase III trials would consist of just responders. If we used pharmacogenetics to identify them by Phase IIb, then later studies could potentially be smaller and drugs with higher response rates would result because non-responders would not be able to 'dilute' the response rate. Pharmacogenetics could also be used to rule out those susceptible to side-effects.

In addition, given that Phase IIb trials are designed to refine dosing, their smaller size means that they might not be able to flag up the smaller incidence, but serious, side-effects that often come to light only when a drug is on the market and taken by millions of patients. It was postulated that we could have larger Phase IIb trials, scrapping Phase III and moving straight on to Phase IV.

The cost of adverse drug reactions

Professor Munir Pirmohamed, the NHS Chair of Pharmacogenetics, University of Liverpool discussed his work [2,3]. A prospective study investigating the cause of admission in two hospitals found that 6.5% (n = 1225) of admissions were due to adverse drug reactions; death caused by adverse drug reactions occurred in 0.15% of admissions, equivalent to 5700 deaths per year with an associated cost of more than £446 million per annum to the NHS. Looking at the data in another way, he noted that seven 800-bed hospitals are occupied by patients brought in with adverse drug reactions.

Continuing his comments on the theme of the costs of side-effects associated with drugs, he noted that the NHS in the UK could save money and improve patient care by testing for HLA-B*-5701 before Ziagen therapy in HIV-positive patients. Patients with this genetic variant suffer severe skin hypersensitivity reactions, and the strong association has been demonstrated in both retrospective and prospective studies. In a study, incidence of hypersensitivity was reduced from 7%, 12% and 7.8% to <1%, 0% and 2% in clinics in Australia, France and UK, respectively. Use of abacavir also increased by approximately eightfold. Factors contributing to the successful adoption of this approach include the strength of the association, physicians in this area being amenable to change, an organized patient lobby and the availability of a test.

TABLE 1

Regulatory guidance and reflection papers related to pharmacogenetics

Organization	Paper	Date of final publication
FDA Guidance for Industry	Diabetes Mellitus—evaluating cardiovascular risk in new anti-diabetic therapies to treat type 2 diabetes	December 2008
ICH Concept Paper for Topic E16	Pharmacogenomic (PG) Biomarker Qualification: Format and Data Standards	April 2008
CHMP Reflection paper	Use of genomics in cardiovascular clinical intervention trials	November 2007
CHMP Reflection paper	Use of pharmacogenetics in the pharmacokinetic evaluation of medicinal products	May 2007

The issue of patient samples

Another topic that was much discussed was patient samples. This is a very basic part of the puzzle about which to be concerned, and to do large-scale pharmacogenetics studies, large and reliable collections are needed. These are often taken routinely in clinical trials but not often interrogated for genetic information. The questions were raised of whether companies can afford to interrogate the samples, and if they can, is it clear yet what genetic questions are they asking? In addition, do companies take and store samples consistently so that any data obtained is comparable? There are also issues around informed consent, and the difficulty of exporting samples from territories such as China—territories that are expected to drive much of the future growth of the pharmaceutical sector and whose populations are expected to have significant genetic differences to those of the West.

Not all genetic variants have a large effect

Professor Patricia Munroe from Bart's and The London, in her comments on the genetics of hypertension, highlighted how there is a lot of work to be done before genetic research provides easy answers to cardiovascular disease. In this area, there is a need both for new drugs and for a better understanding of cardiovascular genetics, and it is interesting to note that heart conditions are, in general, 30–50% influenced by our genetic make-up and 50%–70% influenced by lifestyle factors. Studies have found genetic variants associated with hypertension, with the genes encoding relevant proteins such as ion channels and calcium ATPase, but the key question is how much these variants contribute to disease. She described how, via the work (including genome-wide association studies) of the Global Blood Pressure Gene consortium and others, 13 genetic variants related to blood pressure were identified, based on the analysis of many thousands of samples. However, each of those variants only explained a small proportion of the total variation in systolic and diastolic blood pressure. They were responsible for around 0.5–1.0 mm Hg of change. Given that a change of 2 mm Hg results in a 6% reduction in stroke, the effect of these variants is minimal at a population level but might be significant at an individual level. New therapeutic targets, therefore, are needed, as are more predictive biomarkers for drug discovery and patient selection, and there is a clear need for identification of variants that have a greater effect on clinical outcomes.

'Early' is a key word

The need to engage early was one of the themes to recur frequently throughout the conference. It will be a key factor in the new paradigm, with early consideration of factors likely to impact drug response (efficacy or risk of adverse events), early engagement with key stakeholders (regulators and reimbursement authorities) and building responder analyses into early clinical development plans. This means early engagement by pharmaceutical and biotechnology companies with genetics experts so that the full potential of pharmacogenetics is realized.

Is pharmacogenetics welcomed by the industry?

The biopharmaceutical industry is struggling to fill the revenue gaps caused by massive patent expiries—so much so that many commentators are starting to believe that the age of the mega-blockbuster is over, to be replaced by that of the 'minibuster'. The minibuster would still generate sales of billions of dollars, but only in the population in which it is known to be effective—and in the new cost-effectiveness-driven world, would be reimbursed. Initially, though, will industry welcome technologies that mean that their drugs are directed at smaller markets?

Other areas of consideration

Other issues addressed at the conference include bioinformatics and subgroup analysis of clinical data. The increasing amounts of genetic and pharmacogenetic data generated need to be managed by improved bioinformatics tools, so that they can be used efficiently by all players. To obtain subgroup analysis data from early clinical development studies, these need to be designed statistically to be sufficiently powered and will also need to use innovative statistical methodologies. Sustainability for pharmaceutical companies will only come from effective networking, partnering and collaborations in order to gain the expertise and access to the resources they need to exploit the enormous knowledge emerging from genetic studies, and the importance of strengthening interactions between academia and industry has been recommended in numerous recent reports [4,5].

Concluding remarks

Although genetics and pharmacogenetics are not the cure to all the ills that ail the industry, they are a powerful piece of the jigsaw.

References

1 Challenge and opportunity on the critical path of new medical products. FDA White Paper 2004
2 Pirmohamed, M. *et al.* (2004) Adverse drug reactions as cause of admission to hospital: prospective analysis of 18820 patients. *BMJ* 329, 15–19
3 Hughes, D.A. *et al.* (2004) Cost-effectiveness analysis of HLA B*5701 genotyping in preventing abacavir hypersensitivity. *Pharmacogenetics* 14, 335–342
4 The stratification of disease for personalised medicines. ABPI White Paper April 2009
5 Genomic Medicine. House of Lords, Science and Technology Committee Report July 2009

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