AN AUDIENCE WITH...

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Allen D. Roses, M.D., FRCP (Hon), was appointed as Senior Vice President for Genetics Research at GlaxoSmithKline in 2000. In 1997, Roses joined Glaxo Wellcome after leaving Duke University and was charged with organizing genetic strategies for susceptibility gene discovery, pharmacogenetics strategy and implementation, and integration of genetics into medicine discovery and development. Roses was one of the first clinical neurologists to apply molecular genetic strategies to neurological diseases, and played a part in the identification of the chromosomal location of genes involved in more than 15 diseases, including several muscular dystrophies and Lou Gehrig's disease. He also led the team that identified apolipoprotein E as a major susceptibility gene in common late-onset Alzheimer's disease, a now widely confirmed finding.

Now that the FDA is in the process of finalizing its guidelines on pharmacogenomic data, when do you think we will see the first drug approvals dependent on supporting pharmacogenomic data?

I believe that 'finalizing' the FDA guidelines is a bit strong. These are some initial guidelines for submitting data that will no doubt be modified as the FDA gains more experience over the years with pharmacogenetic (PGx) and pharmacogenomic data. The establishment of the Office of Clinical Pharmacology and Biopharmaceutics with senior experienced FDA leadership will provide prospective guidance for funnelling PGx data to the therapeutic areas. This is a major administrative and scientific leap forward. My own bias is that the road to safer and more effective medicines will be paved with PGx data, and the genie is out of the lamp — and the FDA is way ahead of the thinking of most pharmaceutical and biotech companies.

Is GSK's approach to its pipeline changing in the light of the genie's emergence?

GSK has anticipated the effect of the Human Genome Project across the pharmaceutical pipeline. Traditionally in drug discovery, confidence building for targets went through a three-to-seven-year period of 'target identification and validation' before committing to screening chemical libraries. By identifying tractable targets associated with human disease patients (example: 6,500 single-nucleotide polymorphism (SNPs) from 1,400+ tractable targets tested for association in 500 patients and 500 controls), the number of targets that can be screened rapidly increases. By increasing the resources for chemical screens, genomic and other validation can be focused on post-screen leads — rather than on building confidence around targets over several years. Pipeline flow and efficiency is increased greatly (the "quantal step-up in discovery" referred to by Mark Fishman in last month's *An Audience With...*). However, the true validation of an asset comes with clinical efficacy demonstrated in Phase II trials. There are three types of clinical efficacy studies: those with clear efficacy, those with none, and those with a partial positive signal — but usually not enough to move forward with clinical trials. Efficacy PGx provides a means of identifying a subgroup with the highest chance of non-response, so that subsequent studies can be enriched for success by eliminating 'non-responders' in subsequent trials. Attrition is decreased by enabling less costly clinical trials to proceed.

So do you expect the first clinical application of PGx to be in the early elimination of non-responders from trials?

An illustrative example comes from a molecule being evaluated for treatment of obesity, where weight loss over the clinical trial is the endpoint. The FDA has provided guidelines for efficacy and, in one trial, there were approximately 25% of patients who exceeded these guidelines. In addition, there were also drug-treated patients who gained weight. Using SNPs from candidate genes related to the mechanism of the molecule, several homozygous SNPs were found in the group of efficacy patients, whereas the weight-gain group were homozygous for the other allele. Heterozygotes segregated in-between. Thus both cohorts of patients are identified by distribution of SNP alleles. In an ongoing Phase IIB clinical trial we are evaluating the effect that the elimination of non-responders would have on the size of subsequent Phase III trials.

Is it possible to predict whether SNP-based rationalization is likely to be a common feature of the Phase III trials of the future?

With all the hype during the past decade about the immediate impact of genomic data on drug development, I would prefer to project from a database of pipeline studies, than predict from the first successes. The importance today is that efficacy PGx can provide confidence and economy for continuing development, rather than sudden pipeline attrition of an effective molecule. Phase IIA efficacy PGx fits the 'fail early, fail fast' mantra heard in pharmaceutical R&D in recent years, and by selecting molecules with promise, subsequent trials can be smaller and less expensive, if non-responders are excluded from subsequent studies.

And as for safety PGx?

Hyperbilirubinaemia that occurred during a large Phase III trial was explained by a variant of the *UTG1A1* gene, which was identified during the trial. Fifty percent of people carrying the 7-7 polymorphism became hyper-bilirubinaemic during the trial. When the trial was completed and the code broken, those with the 7-7 genotype but no adverse events were in the placebo group[1]. The identical PGx data were presented to an FDA Advisory Committee for atazanavir, a marketed Bristol-Myers Squibb drug. So safety PGx is already making contributions. There are now several other examples and the critical question is 'How few patients does it take to profile an adverse phenotype accurately?' We have demonstrated in our trial that genome-wide scanning at a density of 100,000–200,000 SNPs could accurately select patients at high probability with ~10–20 patients. Therefore, safety PGx methods can reduce attrition and reduce risk of many effective molecules during late development and post-marketing.

1. Roses, A. D. Genome-based pharmacogenetics and the pharmaceutical industry. *Nature Rev. Drug Discov.* **1**, 541–549 (2002).