Pharmacogenetics: Personalised Safety and Segmented Efficacy

Summary of the lecture given by Dr Allen Roses on 31 March 2003, on the occasion of the launch of the Academy Forum

Dr Roses' vision is that by 2010-2015, SNP-based pharmacogenetic testing will be standardised for the population and the data will be routinely available in primary care for targeting an appropriate drug on the basis of sufficient efficacy and personalised safety.

Human genomics research will have major impact on medical practice in many ways. Some of these impacts will not be immediate – the application of genomics research to finding and validating novel disease targets will require about a decade for medicine development. By contrast, as Professor Roses emphasised, the application of whole genome pharmacogenetics will rapidly yield better-targeted medicines, "the timeline for applying whole genome pharmacogenetics is now".

MAPPING SNPs – A NEW MODEL FOR RESEARCH COLLABORATION

Initiation of the Single Nucleotide Polymorphism (SNP) Consortium was a landmark in the development of resources for the genome-wide scanning of individual variations in coding sequence – underpinning the development of pharmacogenetics. The productivity of the SNP Consortium in discovering and mapping considerably more SNPs than originally expected – and under budget – exemplifies the importance of building new types of international collaboration between public and private research groups (progress was also accelerated in consequence of the faster than expected sequencing of the human genome; that represented a different sort of public-private relationship – a race).

SNP MAPPING AS A CRITICAL TOOL FOR BIOMEDICAL RESEARCH

The application of pharmacogenetics in generating medicine response profiles is already rapidly evolving. Until now, the candidate gene approach has been based on the testing of specific hypotheses about the role of genes in the drug response – the number of variants is necessarily limited experimentally but also constrained by the researcher's ability to generate hypotheses. For the future, constructing SNP profiles from whole genome scans and matching with clinical events is not limited by prior assumptions and will, itself, be productive in generating hypotheses.

GENE VARIENT – DISEASE ASSOCIATION: PIONEERING STUDIES ON APOE4 – ALZHEIMER DISEASE

The example of apoE4 – a susceptibility gene variant for common forms of Alzheimer disease – provides a good illustration of the increasing power of SNP mapping as a fundamental tool in medical research. The initial research on apoE4, demonstrating that the average age of onset of Alzheimer disease varied according to genotype, was a major advance in understanding the disease but required several years of research from the earliest identification (1993) until definitive validation (1996-7). A re-examination of this association by high density SNP mapping of the apoE region in Alzheimer patients by disclosed multiple SNP associations across the coding region for apoC1 and apoE. Thus, the gene associated with Alzheimer disease could have been found in months by this technique rather than the years that it did take by using conventional association

studies. Today, with access to markers across the whole genome, an equivalent association would be detected within days. The rate-limiting factor in identifying disease-associated gene variants has become the availability of well-phenotyped patient material collections, but rapid research advances can now be expected.

ROLE OF PHARMACOGENETICS RESEARCH IN UNDERSTANDING DRUG EFFICACY AND SAFETY

Association of SNP profiles with phenotypic variation can be applied in pharmacogenetics to clarify patient variability with regard both to the efficacy response to a drug and the occurrence of side effects. The primary goal for the pharmaceutical industry application of pharmacogenetics is personalised patient safety. Personalised efficacy is unlikely to be achieved so precisely as safety because of a gradient of therapeutic efficacy and the placebo effect – thus the population would be segmented for efficacy, rather than individualised. Some have raised concerns that the application of pharmacogenetics to efficacy will fragment the commercial market. However, identifying those population subsets that respond well to a drug (enriched efficacy) should provide a lower attrition rate during the pharmaceutical R&D process so increasing the number of products in the pipeline (while also enabling smaller, more rapid clinical trials). The net effect is predicted to be increased availability of efficacious drugs for a segmented market.

CREATING NEW INDUSTRY STANDARDS

In considering the potential for the application of pharmacogenetics to pharmaceutical R&D and the pipeline, phase II trials can be conducted so as to identify the SNP profile for efficacy; smaller, more efficient phase III trials will result in approval of a product with a defined efficacy medicine response profile. Comprehensive post-marketing surveillance could then identify the adverse event response profile more effectively than the current reliance on clinical development programmes – creating a new industry standard in both efficacy and safety.

PROOF OF PRINCIPLE: ABACAVIR

A pioneering example of such research, using whole genome mapping is provided by Abacavir – a highly effective drug with a significant incidence of hypersensitivity adverse events. In response to European Regulatory Authority requests, GlaxoSmithKline (GSK) has been examining SNP profiles to differentiate between the control and adverse event phenotype: for the Abacavir proof of principle, GSK has worked with the Regulatory Authority in markers of increased risk. The SNP profile disclosed association of the hypersensitivity reaction with two candidate genes: TNFalpha-238 and HLA-B57. This association was recently confirmed by a research group unconnected with GSK – illustrating the point that if pharmaceutical companies do not embark on such research for their own products, then others will.

DEVELOPING USABLE CLINICAL TEST TO PREDICT ADVERSE EVENTS

GSK research on the HLA-B57 association with Abacavir hypersensitivity has continued, so as to define variation among ethnic subgroups of the population and, with Perlegen, empirically to explore SNP variation at other loci across the whole genome (using high density mapping with 1.7 million SNPs). Numerous associations have been revealed – some will be false positives – and others have potential value in designing diagnostic profiles. The goal is to combine a small number of SNPs to create a useable clinical test that will reliably predict the adverse event, i.e. it must have high specificity and high sensitivity in all the major ethnic groups. It is anticipated that such tests will enter medical practice within 5 years.

IDENTIFYING ENRICHED EFFICACY IN REAL-TIME

Another GSK example of the potential application of pharmacogenetics was furnished by an anti-obesity drug that, during a 6-month phase II “all comers” trial, appeared overall less efficacious than the gold standard comparator drug. However, some patients receiving the GSK compound responded much better than the gold standard, and efficacy in this subset of the population was found to be associated with variation in three SNPs. The GSK compound was discontinued for other reasons but the case history illustrates the contribution of pharmacogenetics to real-time decision-making, and to the education of the Regulatory Authorities.

EXTENDING THE VALUE OF PHARMACOGENETICS RESEARCH TO ALL DRUGS

The issue was raised (and revisited during discussion) that while pharmaceutical companies are likely to identify the SNP associations for their own developed products – and consent for pharmacogenetic testing research is now obtained from all patients participating in GSK trials – who will do the equivalent research for OTC or generic products? GSK is providing substantial, unrestricted, resource from its own laboratory for academic researchers but there is a role for public policy makers and public research funders in identifying and progressing the research agenda for those drugs that probably will not be characterised by the pharmaceutical companies. If this societal responsibility is not faced, then there is risk of creating another underclass – those who depend on generic drugs.

In further discussion, Professor Roses reiterated the importance of pharmaceutical companies acting to educate and inform the Regulatory Authorities about the potential of pharmacogenetics. The GSK drug Lotronex provides another example of the company working with the FDA to use pharmacogenetic testing in support of safety. Companies are leading in the application of pharmacogenetics to drug development - the driving force is not how soon the Regulatory Authorities require this information but rather the prospect of differentiating commercial value for drugs with predicted safety.

EXPRESSION PROTEOMICS: RE-INTERPRETING ALZHEIMER DISEASE PATHOLOGY

Dr Roses’ presentation also covered the increasing importance of expression proteomics, again exemplified by work on apo E. Expression profiling to compare wild type and apo E-knock out mice identified the concomitant regulation of other proteins. In apo E-knock out mice, 5 enzymes involved in the glucose metabolic pathway are significantly increased or decreased in abundance (additionally, polymorphism of glutatione-S-transferase is associated with age of onset of Alzheimer disease). Confirmation of the role for glucose metabolism in symptomatic Alzheimer disease is drawn from an earlier PET studies with fluorodeoxyglucose – showing decreased brain glucose utilisation by comparison with age-matched controls. Furthermore, decreased brain glucose utilisation was also found in volunteer apo E4 homozygotes studied, on average, 20 years before the onset of overt Alzheimer disease. This research identifies the possibility of correcting Alzheimer disease by influencing brain glucose metabolism and a GSK compound is now entering clinical research.

During the discussion session, many other issues were pursued: the relative roles of pharmacogenetics and pharmacogenomics in cancer research; whether cost was an issue in the application of pharmacogenetics to medical practice; the likely importance of proteomics in studying effects of ageing; the pathobiology underlying adverse events. There was general agreement that the quality and importance of this Forum launch presentation and the vigour of the discussion inspired augured well for the future of the Forum.

Related articles (links are to pdf files)

1. Roses, A.D. The genome era begins… *Nature Genetics Supplement*. **33**:217 (2003).

2. Roses, A.D. Pharmacogenetics place in modern medical science and practice. *Life Sciences*. **70**:1471-1480 (2002).

3. Roses, A.D. Medical applications of haplotype-based SNP maps: learning to walk before we run. *Nature Genetics*. **32**:353 (2002).

4. Roses, A.D. Genome-based pharmacogenetics and the pharmaceutical industry. *Nature Reviews*. **1**:541-549 (2002).

5. Roses, A.D. Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. *Lancet*. **359**:1121-1122 (2002).

6. Roses, A.D. 2025: The Practice of Neurology, Back From the Future. A*rch Neurol*. **58**:1766–1767 (2001).

7. Roses, A.D. Pharmacogenetics and the practice of medicine. *Nature*. **405**:857-865 (2000).

Notes:
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