Interview

Pharmacogenomics: past, present & future

Alun McCarthy speaks to Theo Bond, Assistant Commissioning Editor

Alun McCarthy is President and CEO of PGXIS Ltd, and Chief Scientific officer of CytoPathfinder, Inc. PGXIS is a UK-based company that has developed innovative technology to analyze large, complex genomic data sets. This approach, called Taxonomy3, has a number of benefits over conventional analysis methods. These include: more statistical power to find associations; the ability to identify gene–gene interactions; greater predictive power; and integration of different data types in a single multivariate analysis.

■ How did you first become interested in pharmacology and, in particular, pharmacogenomics?

I trained as a protein biochemist and was involved in research at Dundee University (Dundee, Scotland) but I became more interested in applied rather than pure science. While working and publishing on protein biochemistry, I just had this nagging feeling that nobody would really notice if I had never done it. At the same time GlaxoSmithKline (although just known as Glaxo at that time) was setting up its biochemistry department and I was invited to join. This fitted very well with what I wanted to do, so I joined Glaxo and became involved in pharmacology from there on in.

I joined Glaxo in 1984 and was initially working in drug discovery in cardiovascular metabolism. However, I became involved in genetics and in particular pharmacogenomics in the mid 1990s, when Allen Roses' group published work showing that *ApoE* genotypes affected Alzheimer's disease susceptibility. As I had experience working on lipoproteins, I was seconded to spend a year with the Alzheimer's disease group at Glaxo. While I was working on Alzheimer's, there was a series of posters in meetings about how *ApoE* genotypes affected a patient's response to Alzheimer's disease treatment, which I thought was fascinating and pretty cool. Subsequently all those Alzheimer's disease claims have turned out to be false but the principal is still valid. From there on in I moved to working on the development of pharmacogenomics and the latest biomarkers, and have stayed in that field ever since.

■ You have been working in the pharmaceutical industry for 25 years – what have been the greatest advancements in this field since the start of your career?

When I started at Glaxo, molecular biology was in its infancy. Now we have DNA sequencing, RNA expression levels, proteome analyses and all sorts of wonderful technologies at our disposal. The other big change is people's understanding that diseases are not comprised of homogeneous groups of patients; instead they are very heterogeneous, and understanding that heterogeneity is very important if you want to find a new medicine or treatments.

■ How has the introduction of pharmacogenomics changed pharmaceutical development?

Pharmacogenomics is part of the broader change we have seen, where people are moving away from thinking about blockbuster drugs in homogeneous patient groups and more about targeted personalized drugs in identified patient subgroups. I think pharmacogenomics was the vanguard of this, and probably set the scene for all the other types of biomarker work, such as imaging, gene expression and proteomics, that has been going on since. The other impact that I think has been brought about by this change in attitude is how regulatory authorities interact with each other. For example, these days it is very common to see the US FDA and the EMA having joint meetings, sharing information and so on. This did not happen as much back in the 1990s. It was the regulatory authorities' mutual concerns that they didn't understand enough about the

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latest developments in pharmacogenomic science that instigated them to talk to each other and set up joint briefing meetings and so on. So, I think it has changed how the regulatory authorities and companies interact, which they have now extended to a number of different areas.

■ **You are Chief Scientific Officer for Pharmacogenomic Innovative Solutions (PGXIS Ltd), can you tell us about the company and what it does?**

I was one of the cofounders of the company, which we established in 2007, and we are the UK part of a company that is registered in Japan: this involves a lot of early morning teleconferences, but also has its benefits in that every few months I get to eat sushi in Tokyo. PGXIS is comprised of genomics, bioinformatics and pharmacogenomic experts, and we provide two main services: first we have pharmacogenomic consultancy activity, where we make our expertise available to small/medium-sized pharma and biotech companies. All the large pharmaceutical companies have their own pharmacogenomics groups. The small/medium companies do not have that luxury, so we work with them and support a whole range of activities from operational issues such as what a consent form should look like, where you should store the samples and so on, through to designing and analyzing the studies. In addition, we also address more strategic issues about where in their portfolios these companies should be applying pharmacogenomics. That is one part of what we do: a more substantial part is that we have been developing a novel genomics analysis method called Taxonomy3, which was coinvented in 2005 by our Head of Clinical Sciences, Olivier Delrieu. We have been very impressed with this method; in fact it has delivered more than we expected every time it has been used. The reason it can produce such fantastic results is that it allows broad analysis of gene–gene interactions. This is very important as these interactions are thought to be one of the explanations for the missing heritability that occurs in a large number of genome-wide association studies. Being able to look at those interactions provides more genetics information, which gives more genetic

insight. Therefore, PGXIS do this as fee-for-service work for other organizations if they have access to genetic data sets that they would like us to analyze.

We have now realized that Taxonomy3 is so good that it can be used as a drug discovery tool. A conventional genome-wide association study will give maybe one to three peaks at best in a Manhattan plot and this does not really tell you about the underlying biology. Using our Taxonomy3 method we can discover a lot more genes that interact. For example, in one data set we looked at, conventional analysis identified one peak in the MHC region on chromosome 6, whereas Taxonomy3 identified 48 other genes outside this region. So, the analysis of a disease population will give 40/50 genes genetically linked to the human disease. Because of this association with human disease, drugs based on targets derived from this output are much more likely to be successful in Phase II clinical studies. Therefore, it is a matter of finding out which of those output genes are druggable and identifying compounds that act through these targets. We are looking to shift the direction of the company from being a company providing fee-for-service work for other organizations to become a drug discovery company using the tremendous genetic insight that we are able to access using the Taxonomy3 analysis method.

■ **What ethical issues are raised as pharmacogenomics progresses as a diagnostic tool?**

There are probably three main ones. First, it is obvious that if you are analyzing DNA you are generating genetic data, which automatically come with sensitivities and ethical issues about predictions, impact on family members and so on. Second, there is the broader issue of equality of access to treatment. If you can use genomic data to test the probability that an individual will respond to a medicine, then the healthcare payers are very keen to know that and will want to target medicine to groups where there is a higher probability of success. The issue is that these markers are never black and white, and you will never identify a group of patients who will always/never respond to a particular drug. There will always be some people in each group

who will/won't respond. However, if the response rate is too low then it might not be cost effective to treat a particular patient group. So, there are a number of issues around individuals who would respond to a particular treatment but who are not able to receive the treatment because their genetic analysis suggests that it would not be cost effective. This is an issue that people are still grappling with. Clearly you would need to make the predictive power of pharmacogenomics as high as possible but it is never going to be 100%. A third area with ethical issues is to do with ethnicity because genetic information, and the impact of genetic variables in particular, varies in different ethnic groups. The overwhelming majority of data generated in this area are in Caucasians, so there is a dearth of data in other ethnic groups. This is important because even when you have very good predictors for drug response (e.g., *HLA-B*5701* and drug hypersensitivity), the predictive power varies in different ethnic groups. Making sure these predictions are right for different groups is going to be a big issue going forward. How can we make sure we understand how these markers work in different ethnic groups? And how to make sure different ethnic groups are not excluded from or disadvantaged in basic research are important areas that need to be addressed.

■ What are the major challenges in translating pharmacogenomics in the clinic?

There are a number of challenges; a key one being how predictive are the data? This is important in defining the clinical utility, which has traditionally been very difficult to do. It is relatively easy to carry out a retrospective analysis and find a genetic association with a particular outcome. It is much harder – and more expensive – to carry out a prospective study to understand how that test could impact clinical outcome and show benefit to the patient. This is a big gap in the available data, and it has been a big gap for many years.

The second issue is the infrastructure that would enable pharmacogenomic sampling, data analysis and interpretation within the context of clinical treatment. Pharmacogenomics will change the way individuals are treated away from the

standard system where the doctor examines the patient, diagnoses the disease and prescribes treatment. Instead, we are taking samples that are sent off, analyzed and the results returned. How does this fit into the way the healthcare system works? Who is going to interpret these data? Is that carried out by the testing laboratory or the physician? So there are a number of issues concerning the infrastructure, training and the utilization of the algorithms, all of which may differ in different countries.

The disease area where the pharmacogenomic process has grown rapidly is oncology, at least partly because the infrastructure problems are not so much of an issue. It is routine to take samples, it is routine to have them analyzed and routine for the results to come back to the doctor to guide therapy. So, pharmacogenomics fits very well in the treatment protocols in oncology.

The third challenge is the integration of different data sets. Up to now it has been assumed that one or two proteins, genetic variants or expression levels will be all you need. Again, in an area like oncology this has been true, where there are sets of cancers with gene disorders such as *BRAF*, *KRAS* and *EGFR*, among others. However, in more complex diseases, there are many more factors involved and to generate the predictive power needed to determine drug treatment will almost certainly involve looking at more factors than just one gene or one protein. It may be a range of proteins, coupled with a range of genetic variants or gene expression levels. I think the challenge of identifying those more complex predictive marker sets and the infrastructure are the two major challenges to be overcome the next few years.

■ How will the field of pharmacogenomics develop in the near future?

I think there will be a lot of work on the integration of large data sets and that is going to be a particularly important development. Our Taxonomy3 method, for example, can handle large data sets incorporating genetic data, expression levels or clinical parameters, and I know other groups are working on similar types of approaches. So, that is a challenge that

will start to be addressed. The other area that will be key in the near future is next-generation sequencing, which is capable of producing large amounts of data. The challenge now is to analyze and interpret the data and see to what extent this technology can move out of the laboratory into clinical practice. Our ability to analyze the data is lagging well behind our ability to generate it.

I think pharmacogenomics has to be seen in the context of the other ways of targeting identifiable groups of patients. Protein biomarkers, gene-expression levels and imaging are all part of the same approach. They are all looking to differentiate patients into subgroups, and then find ways to target the appropriate treatment.

I see pharmacogenomics as part of that broad spectrum.

Disclaimer

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