Company Profile

PGXIS Ltd

Pharmacogenomic Innovative Solutions Ltd (PGXIS) was established in 2007 by a group of pharmacogenomic (PGx) experts to make their expertise available to biotechnology and pharmaceutical companies. PGXIS has subsequently established a network of experts to broaden its access to relevant PGx knowledge and technologies. In addition, it has developed a novel multivariate analysis method called Taxonomy3 which is both a data integration tool and a targeting tool. Together with siRNA methodology from CytoPathfinder Inc., PGXIS now has an extensive range of diverse PGx methodologies focused on enhancing drug development.

KEYWORDS: drug development ■ personalized medicine ■ pharmacogenetics ■ siRNA ■ Tax3 analysis

Pharmacogenomic Innovative Solutions Ltd (PGXIS, UK) was established in May 2007 in southeast England as the UK operation of PGIS Inc., registered at the same time in Japan. The company was founded by pharmacogenomic (PGx) experts with experience in the pharmaceutical industry: this complemented the diagnostics and pharmaceutical industry expertise in PGIS Inc. very well. The companies provided PGx consultancy for a number of pharmaceutical companies around the globe, in particular, helping those companies without an in-house PGx group to incorporate the technology into their drug-development pipeline. Although PGx has been a growing science for a number of years, the speed of uptake by pharmaceutical companies varied widely for many reasons:

- The regulatory environment was uncertain and there were a number of scientific challenges;
- The associated ethics issues raised concerns; there was debate over the possible commercial impact of patient stratification using PGx-based biomarkers;
- The necessary skills were in short supply. Therefore, PGXIS was established to provide these necessary skill sets for incorporating PGx into drug development.

The consultancy support provided by PGXIS largely consisted of three main activities:

- Helping companies with the necessary processes and documents to implement PGx;

- Assessing development portfolios to identify projects where PGx will add significant value to them;
- Advising on experimental design and analyzing the resulting PGx data.

Pharmacogenomic Innovative Solutions Ltd has not set up a genotyping laboratory to complement its PGx support activities as there are an ever-growing number of highly competent genomic companies who can provide a wide range of quality analyses when required. By not committing capital resources to establish a genotyping laboratory, PGXIS is free to tailor the experimental design (and hence the preferred technology solution) to meet the specific objectives of their client companies.

It is important that PGXIS can access the necessary wide range of specialist expertise when needed. To ensure this, a network of experts was established in such areas as statistics, genetics and medicine. The knowledge of these experts could be brought to bear on any particular program depending on the needs of that program. By tapping into this additional knowledge base, the company is able to provide a much broader service to its clients and address PGx issues in a wide range of therapeutic areas.

To develop the business further, it was important to broaden the range of PGx-related technologies that the companies could offer: so far, this has been achieved in two ways. First, PGXIS invested significantly in the development of a novel analytical method called Taxonomy3

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(Tax3). This method was originally devised in 2005, one of the originators being Olivier Delrieu, our head of Clinical Sciences. Tax3 was developed to allow multivariate analysis of genetic datasets, and the theoretical basis of Tax3 is supported by a number of peer-reviewed publications in conjunction with academic statisticians [1–6]. While the method is ideally suited to large, complex genomic datasets, the original software and algorithm was only able to manage small datasets (e.g., see [7]), and was not able to handle the large datasets available today. PGXIS has developed the software so that the method is able to handle the large, genome-wide data that are routinely generated with the latest analytical technology.

Tax3 can be applied to large case–control studies including variables of all types: discrete (SNP and categorical) and continuous (omics and clinical). The method, which performs multivariate analysis of variables, has the following key features:

- Targeting tool, addressing complex disorders and human heterogeneity;
- Data integration tool, analyzing genetic and nongenetic data at the same time.

The Tax3 method has a number of advantages over conventional (univariate) analysis methods:

- Greater statistical power: it is clear that the method can identify significant associations that are not detected using more conventional univariate methods;
- Ability to analyze data at the SNP, gene or even pathway level. Analysis at the gene level has shown to be more robust than analysis at the SNP level by reducing the impact of any aberrant or poorly genotyped marker;
- Interactions between variables (e.g., gene–gene interactions) can be carried out using the method. This has proved a valuable method for identifying additional variables of interest, and to elucidate pathways of interest;
- Different datasets can be assessed using the same log bay factor methodology, so genetic, genomic, proteomic and clinical data can all be analyzed at the same

time. With the expansion of genomic technologies, this feature of Tax3 will become increasingly important;

- The method can be used for whole-genome prediction where all the available data can be used to assign case–control labels to an unknown sample;
- Graphical output that aids communication of results to nonstatisticians.

These features and deliverables make Tax3 a powerful new method for analyzing the large, complex datasets that are generated today. The method is very suitable for identifying patient subgroups, and the markers that define them, making it an excellent tool to facilitate the development of personalized medicine.

The second technology accessed by PGXIS arose in June 2009 when PGIS Inc merged with another small Japanese firm, CytoPathfinder Inc. (CP; Tokyo, Japan): the resulting company retained the name CytoPathfinder Inc., and PGXIS became the UK operation of the newly merged company. CP, founded in 2004, has developed an advanced solid-phase transfection methodology, which is particularly valuable for siRNA studies as high levels of transfection and gene knockdown, but low levels of cytotoxicity, are possible [8–10]. The critical step involves the use of a transfection accelerator to facilitate the entry of the siRNA into cells, increasing the efficiency of the knockdown. The method has a number of advantages over more conventional methods:

- The high transfection efficiency means that fewer cells are needed for a robust signal. This allows 1536-well plates to be used routinely, leading to higher throughput and making genome-wide siRNA screens much more accessible;
- This higher sensitivity is also very important for allowing studies where the number of cells is limited, such as primary cells from individual tumor samples;
- The methodology is effective in cells that are difficult to transfect using more conventional methods, such as primary cells including neurons;
- The high efficiency and low toxicity means that double knockdowns are very

feasible, greatly facilitating new discoveries of synthetic lethal and other combination treatments.

CytoPathfinder's siRNA methodology is made available to drug-discovery and -development organizations for a number of purposes. These include: pathway analysis as a key part of target identification and validation; and synthetic lethal studies looking for effective drug combinations. CP makes this worldclass technology available to third parties in a variety of ways: fee-for-service research; provision of reagents for analysis; and technology transfer to the third parties.

The area of most interest to PGXIS however is the use of the siRNA methodology to identify candidate genes for PGx analysis. For PGx to be incorporated into clinical development as early as possible, data must be generated in Phase II studies. However, the relatively small size of these studies limits the number of variables that can be analyzed – otherwise there is a good chance of false-positives (if no correction for multiple testing is applied) or false-negatives (if multiple testing correction is applied). Therefore, it is imperative to identify the most relevant candidate genes for any prespecified PGx analysis. As long as the drug under development generates a phenotype in a cell-based assay, broad

(including genome-wide) siRNA knock-down can be used to identify the genes that modulate drug action, which then form a candidate gene list for clinical PGx studies. This avoids the usual process of defining candidate genes which relies on assumptions about pathways, drug action and so on. This rigorous method for determining relevant genes for PGx analysis clearly synergises with the clinical PGx capability of PGXIS.

This range of technologies available to PGXIS impact a number of stages of drug-discovery and -development with a strong focus on the early-development stages, where attrition is the most problematic and where PGx can make an important contribution to increasing research and development throughput (see FIGURE 1).

Future perspective

There are a number of features that will drive the future activities of PGXIS:

- The general level of PGx activity will increase as more precedents are established and as more regulatory authorities finalize guidance documents. For example, the draft EMA guidance on PGx and pharmacokinetics will require PGx data under certain circumstances. As drug-discovery and early development becomes more and more the preserve of small biotechnology and

Figure 1. Synergy of Pharmacogenomic Innovative Solutions technologies in early clinical development.

academic groups, there will be an increasing need for PGx support to these organizations.

- The increasing safety consciousness of regulatory authorities will put increasing pressure on pharmaceutical companies to study the PGx of these adverse events in an attempt to limit the incidence of serious side effects.
- Concerns over drug pricing and reimbursement will drive companies to adopt PGx and other technologies leading to personalized medicine.
- Pharmaceutical and biotechnology companies will continue their trend for outsourcing, accessing specialist expertise (such as PGx) from external companies.
- An increase the efficiency of PGx studies will be important particularly in Phase II, and PGXIS's association with CP can exploit the latter's siRNA technology to produce viable candidate genes.
- The strong trend to deliver personalized medicine will open up a range of opportunities for the Tax3 software to identify patient responder subgroups.

A number of challenges will still need to be overcome for PGx to make its full contribution to drug development and utilisation. PGXIS (together with its partner CP) has now aggregated the necessary key skills to maximize the impact of PGx on drug development, particularly in Phase II, where most of the attrition occurs. As such, the company is now well placed to look to develop its business strategy to include in-house drug development alongside its consultancy activities, applying the synergistic PGx technologies at its disposal. PGXIS is already looking for potential development candidates which would most benefit from application of the company's technology.

Financial & competing interests disclosure

Alun McCarthy is an employee of PGXIS Ltd and a shareholder and board member of CytoPathfinder Inc. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Highlights

- Pharmacogenomic Innovative Solutions Ltd (PGXIS) was established in 2007 by a group of pharmacogenomic (PGx) experts to make their expertise available to biotech and pharmaceutical companies.
- PGXIS has established a network of experts to broaden its access to relevant PGx knowledge and technologies.
- The company has invested in the development of a novel multivariate analysis method called Taxonomy3. This is both a data integration tool and a targeting tool that provides valuable additional outputs for implementing personalized medicine.
- siRNA methodology from CytoPathfinder Inc. will enhance candidate gene selection to improve the efficiency of PGx studies particularly in Phase II.
- PGXIS now has an extensive range of diverse PGx methodologies focused on enhancing drug development which can be used to support client organizations and future in-house drug development.

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