Drug discovery in a multi-omics world

Collectively rare diseases affect millions of people worldwide, but the number of people with any one condition is very small. Finding a cure is difficult as the market is not large enough to justify a big investment in drug development. This is all about to change with the development of multi-omics technology, which elucidates the exact cause of a disease and its effect on a specific biological pathway. Once the fundamental biology of a rare disease is established a drug (already approved for another disease) that targets this metabolic pathway could then be repurposed for this condition with relative ease. Additionally, a new drug that failed in clinical trials but showed good results with a small sample of patients could be repositioned as an orphan drug and command a high premium.

By Mike Furness

It has been known for a while that people with different genotypes respond to drugs differently. New knowledge gained from studying rare genetic disease is improving our understanding of the important biological pathways, creating the opportunity for more effective treatments.

Genomics is changing the landscape of disease diagnosis and treatment and this is now permeating through drug development. Instead of looking for new chemistry the industry is refocusing on getting a better understanding of the underlying biology.

The game changer has been the falling cost of sequencing. In 2003 sequencing a genome would have cost the equivalent of the most expensive house in London, in 2013 this had fallen dramatically to the cost of an Arsenal football club season ticket, according to Dr Ewan Birney, Director of EMBL-EBI.

This cost reduction has made whole genome sequencing more accessible, enabling greater investigation of rare genetic disease.

Insights from rare genetic disease

Collectively, rare diseases affect millions of people worldwide, but the number of people with any one condition can be very small. Finding an effective treatment for these patients has been difficult as the market is not large enough to justify a big investment in drug development.

Additionally the cost of sequencing has meant that genetic testing, until now, has been limited to a single gene, or small panels of genes for known mutations. In the US, the American College of Molecular Geneticists has produced a list of only 46 genes that a clinician can report any genetic abnormalities on to patients. These are genes that have known interventions.

However, the falling cost of sequencing is changing this and it has enabled studies such as the Discovering Developmental Diseases (DDD) project, established between the NHS and the Wellcome Trust Sanger Institute, which has accelerated the development of tools to study omics important in disease.

DNA microarray chip. An example of the technology that is making personalised medicine a reality

DDD was a ground-breaking study which aimed to provide an improved technique for the diagnosis of developmental disease in children. Many of these diseases are life limiting so there is a real need to reach the correct diagnosis as quickly as possible.

Traditionally, disease has been defined by its symptoms and its location in the body. For early developmental diseases this has meant that each symptom is investigated in isolation, by a specialist in that area. The patient is sent from one clinician to another. On average a child with a rare genetic disease will been seen by seven physicians over a five-year period before a diagnosis may be found.

DDD has provided whole genome analysis for around 14,000 children, and their parents, with a previously undiagnosed genetic disease.

The study confirmed that most rare-genetic disease is caused by a mutation in one gene but also that not all mutations result in disease. This is because the protein-coding region makes up only 1-2% of the total DNA and mutations in the 'non-coding' parts of the DNA generally do not have the same level of impact.

This suggests that it is sufficient to use exomes – sections of the genome that code for proteins – to support diagnosis, narrowing the area in which to look for disease causing mutations.

The researchers have further developed the gene annotating system, originally developed within the human genome project, to make it easier for non-specialists to see clearly which genes are associated with disease.

DDD successfully provided diagnoses for around 35% of the families, and identified a 'clinical phenotype' for clusters of affected children, ie those that have similar clinical characteristics and share damaging genetic variants in the same gene. The results have currently been published in more than 15 peer-reviewed journals including a paper in *Nature* linking 12 novel genes to development disorders[1].

Creating clinical phenotypes is very important in progressing knowledge of these diseases. Clinicians may only see one or two cases of a particular disease in their careers, and not all patients with a particular condition will show all the same symptoms. Having access to a reference knowledge-base with which to compare their patient will greatly accelerate diagnosis.

Case study

Bardet-Biedl Syndrome (BBS) is a disease that affects one in 100,000 people in Europe. Symptoms vary depending on the patient, even between siblings, making it a hard disease to diagnosis. Patients normally face a long diagnostic odyssey visiting multiple clinicians and enduring many clinical tests before the correct diagnosis is reached.

One patient had undergone multiple genetic tests over several years for many diseases, including BBS, but they were all reported as negative. Whole exome sequencing was carried out on the patient and the information was analysed using Congenica's Sapientia™ software; a diagnostic platform developed to analyse and interpret whole genome data in a novel way that identifies gene mutations most likely to be associated with disease.

Part of a novel gene, now called BBS7, was found to be missing in the patient (**Figure 1**) and this was causing the disease. Sapientia visually showed this deletion to the clinician. The patient and their family now have a definitive molecular diagnosis so they can plan for the future, join relevant support groups and receive appropriate health, education and welfare provisions.

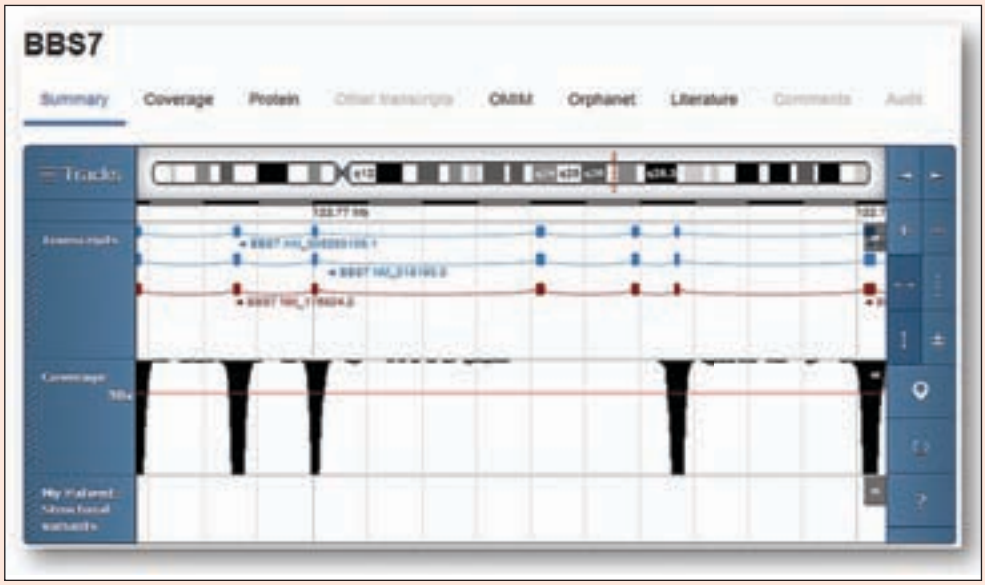

Figure 1: Sapientia visually shows where exon 7 and 8 should be present in a healthy individual (the red and blue boxes) and this is not present in the patient (the black 'cones')

The work in rare-genetic diseases is continuing with the 100,000 Genomes Project, led by Genomics England. The knowledge emerging from this work is significantly advancing our understanding of the causes of disease and has also provided insights into important pathways controlled by the genes involved in these pathways.

Benefits for more common disease phenotypes

The study of rare clinical phenotypes is important as this information can be used to identify therapeutics for more common diseases.

Greater access to sequencing data and improved tools for bioinformatics is facilitating emerging techniques for multi-omics, in which information on the genome, the transcriptome (the RNA that codes the proteins) and the proteome (all the proteins) is combined. With this knowledge it is possible to understand in more detail the biology of the disorder or disease, and the mode of operation of existing drugs. This is revealing new targets for treatment.

A good example of this is the study of rare human bone disorders, which has led to the identification of important signalling pathways that regulate bone formation.

Genetic sequencing machines. *Image courtesy of Sanger Institute, Genome Research Limited*

A balance between creation of new bone and breakdown of the old is necessary to ensure that bones are of the correct shape, size and density.

Sclerosteosisis is a rare, debilitating disease where the bones become thickened and harden causing facial distortion and the build-up of pressure results in blindness and reduced lifespan. It has been found that the condition is caused by a mutation in the SOST gene, which provides instructions for making the sclerostin, a protein that inhibits bone formation.

Only 100 people worldwide are known to have this condition but the knowledge gained from the study has led to the development of a treatment for osteoporosis. In trials a single injection of a monoclonal antibody that inhibits sclerostin markedly increased bone-formation markers in postmenopausal women. The new therapy being developed has an estimated market of 150 million people and a value of $13 billion. Additionally, knowledge of this pathway may provide a new therapy in the small number of people afflicted with this disease for which the current treatment is potentially risky surgery.

Super humans

For some, a rare genetic mutation may give beneficial characteristics and some pharmaceutical companies have started to look for these 'super humans'.

A good example is a chance discovery of an anticoagulant made by Dr Trevor Baglin, Divisional Director of Investigative Sciences and Consultant Haematologist at Addenbrookes Hospital Cambridge, UK, when one of his patients made a miraculous recovery.

Anti-coagulants are given to patients who have previously suffered from thrombosis, but unfortunately these drugs are unable to distinguish between abnormal and healthy clotting. Treatment is therefore a delicate balance between trying to reduce clots while making sure patients do not haemorrhage. The patient was admitted to Addenbrookes Hospital in 2008 with a potentially fatal head injury and symptoms consistent with severe haemophilia. To Dr Baglin's amazement the bleeding stopped and he observed that the phenomenon was down to an antibody in the patient's blood that caused "extraordinary anticoagulation in the absence of bleeding" – preventing lethal clotting.

Dr Baglin called in his colleague Professor Jim Huntington at the Cambridge Institute for Medical Research to design a synthetic version of the antibody and the two realised that they had stumbled upon the "holy grail of anti-coagulant drugs" and a key weapon in the fight against thrombosis and resulting heart attacks. The technology was licensed to X01 Ltd by Cambridge Enterprise, the University's commercialisation arm, and has since been acquired by Janssen Pharmaceuticals in 2015 to address the $20 billion anticoagulant market.

It is examples like this that are changing the dynamics within the industry.

Patient-centred drug development

Unravelling how the mutation affects the metabolic pathways will improve treatments for rare diseases. Known as orphan diseases, more than 7,000 have been identified, of which only 600 have registries (lists of symptoms and other information associated with the disease).

It is the patient support groups, helped by organisations such as EURORDIS (European Organisation for Rare Diseases) and the Genetic Alliance that are beginning to build upon the existing registries.

An emerging trend is for specialists, such as Professor Phil Beales, Head of Genetics and Genomic Medicine at the Institute for Child Health at UCL, UK, Director of the Centre for Translational Genomics and Head of the Cilia Disorders Laboratory, to work with a patient group to build registries in their discipline.

Prof Beales is an expert in Ciliopathies. Cilia are small rod-like structures that are found on the outside of almost all cells. The physiological importance of cilia is still unclear, but they appear to be involved in various signalling pathways. There are several diseases relating to these structures but the diseases are difficult to diagnose, as they are present in almost all tissues there is considerable variation in the symptoms.

For example, the clinical features of Bardet-Biedl Syndrome (BBS) include obesity, rod-cone dystrophy (causing night blindness followed by visual loss in childhood), specific learning difficulties in some but not all individuals, renal dysfunction and a range of secondary features such as extra fingers or toes. There is considerable variation in symptoms even within families. Using whole exome sequencing it is possible to deduce where the mutations lay and the impact they were having on the pathways to produce the clinical phenotypes (see Case Study).

Professor Beales has patients referred to him

Wellcome Trust Sanger Institute; where Congenica is based. *Image courtesy of Sanger Institute, Genome Research Limited*

from across the UK. By using anonymised data, a registry of the clinical phenotypes is being developed. A registry is beneficial to the parents of patients and their consultants as it brings together all the current knowledge of the disease group, its management and therapies and can also provide the opportunity to locate patients for clinical trials.

This is marking a major change in the balance between the pharma companies and the patients.

There is now much greater benefit in bioscience companies working with patient groups. Indeed where a patient group is sufficiently large and well funded it has been able to fund its own drug trials. An example is the Epilepsy Association that bought a high-throughput sequencer specifically for its own research.

Where generics have been used 'off-label' to treat conditions, further research can be used to repurpose these drugs to treat orphan diseases. With the drugs already on the market the time required for trials is much shorter and the resulting treatments can command a premium. There have been several recent examples where the FDA has allowed drugs to be listed following trials with much smaller than usual numbers as the efficacy has been proven.

It is becoming clear that patients with these life-threatening diseases have a different risk profile to other patients and that working with intermediates, such as the patient support groups, greatly enhances the effectiveness of a trial. The Internet has been invaluable in helping patients with rare disease find each other and this is leading to more crowd-sourced data and funding for trials.

Dr Thomas Hiemstra at the Cambridge Patient Led Research Hub at Addenbrookes Hospital is championing this approach. Patient groups are being encouraged to explain the therapy they would like for a particular disease and the reasoning behind this. If there is a sufficient scientific hypothesis, Dr Hiemstra will put them into trials. The advantage of this approach is that there is already evidence of the drugs efficacy and although the pathways have not yet been determined, further research is already weighted towards success.

After a small proof-of-concept trial, the patient group would be in a position to approach the NHS, UK, and say "using this treatment would

References

1 Fitzgerald, TW, Gerety, SS, Jones, WD, Jones, M, van Kogelenbery, M et al. Large-scale discovery of novel genetic causes of developmental disorders. Nature 2015 Mar 12;519 (7542): 223-8

2 The 30-Year-Old CEO Conjuring Drug Companies From Thin Air (9th September, 2015) Retrieved from http://www.forbes.com/sites/nathanvardi/2015/09/09/the-30-year-old-ceo-conjuring-drug-companies-from-thin-air/

save the health service £Xm and we would like a percentage of that to fund further research".

The financial rewards for this approach are already proven. A recent Forbes report (Forgotten Drugs Done Good)[2] gave an overview of drugs that had been shelved by a large pharma but then brought to market by a company with a better understanding of its mode of action. An example is Namenda (Memantine), a treatment for cognitive symptoms such as memory loss and confusion in Alzheimer's disease, originally synthesised by Eli Lilly it was developed by Merz before being licenced to Forest Labs. Sales of the drug reached $1.8 billion in 2014.

Improving success in trials

Recent reports suggest that for novel mechanisms, the likelihood of an efficacious outcome in Phase II trails is around 20%. The high failure rate is often because the drug is only effective in less than 30% of patients. Evidence emerging from multi-omics suggests that if the trials had been stratified it may have been found that the high responders had a similar genotype (Data from Association of British Pharmaceutical Industry) and focussing on these would have made the trial a success.

Stratification is already being used for many cancer drugs. A companion diagnostic has been produced for Herceptin that is used to determine if the patient has a particular variant and for HIV there is HLA testing.

In the future we can see a situation where before treatment is given the patient is genotyped. This would provide the physician with details of which drug metabolising enzymes the patient has and which drugs would work best for that specific genotype, as well as the ones to avoid. This would reduce waste of drugs, highlight the potential of known adverse reactions and, enable the best therapy to be given from the outset. DDW

Mike Furness *has more than 30 years' experience in genomics and is Head of Sales and Marketing at Congenica, a spin-out company from The Wellcome Trust Sanger Institute in Cambridge, UK. Its Sapientia technology is a clinical decision support system for genomic diagnostics, incorporating multi-omics data and personalising therapeutic interventions.*