one nucleus insights

The Impact of Genomics on Drug Development

The first of One Nucleus' high-profile Life Science Leadership Seminars to tackle genomics, and the opportunities it offers for impacting the drug development pathway, took place on Tuesday 11 October 2016. Appropriately, it was hosted by the European Bioinformatics Institute (EMBL-EBI), located on the Wellcome Genome Campus, Hinxton, near Cambridge which is one of the world's most important centres for genome analysis. Speakers from academia and industry reviewed the ways in which genomics, and DNA sequencing technologies in particular, are being used in target selection, drug discovery and development. The seminar also focused on the value of 'big data' and the current and future opportunities, and challenges, that these technologies offer to the pharma and biotech industries.

The speakers included:

- **Jeff Barrett**, Opentargets.org
- **Coralie Vacher**, Illumina
- **Leigh Brody**, Desktop Genetics
- **Anna Gaulton**, EMBL-EBI
- **Michael Menden**, AstraZeneca

Summary of Key Points

Many of the speakers (both from the public sector and industry) covering different discovery stages and therapeutic areas, highlighted some of the following broad factors:

- In 2002, there was one human genome; now there are tens of thousands; by 2025 we may have 100 million individual genomes; and this data must be turned into knowledge that is useful for the health of all
- Collaboration and partnership, perhaps most importantly between sectors, are crucially important: in this era of 'big data' no company or institution can expect to be able to work in isolation
- Open source platforms and open access to data are growing in importance, including in the commercial sector
- The type of 'personalised medicine' that is now being pursued in oncology is now not only desirable, but possible in other indications

Genomics in Target Selection and Validation

The context of this seminar was one in which over 80% of candidate drugs fail to reach the clinic, and many of the failures, even at later stages, are due to a lack of efficacy. It is important to consider how potential drug targets are chosen and prioritised, and high-throughput genome sequencing, a large majority of which is now carried out using Illumina's platforms, has made a huge difference to how this is done. Genome-wide association scanning (GWAS) is proving successful in pulling out targets that are likely to yield useful drugs. The Open Targets initiative, based at Hinxton, has been set up to integrate GWAS data and combine it with publicly available data and experimental evidence to prioritise targets in areas of unmet medical need.

Cancer is one such area in which progress towards genomics-based 'personalised' treatment has been significant in recent years. Developing diagnostic tests to select cancer patients with mutations that are susceptible to, for example, AstraZeneca's Tagrisso™ or Pfizer's Xalkori™ can not only transform the prospects for the individuals concerned but allow the medicines themselves past regulatory hurdles and into the clinic. Significant challenges remain, particularly in rare cancer types where stratification is likely to yield unworkably small numbers in each patient group - almost every childhood tumour type falls into this category. Other therapeutic areas in which progress in defining genetic profiles and patient stratification is being made include inflammatory conditions, including bowel disease.

Genomics in Drug Discovery

Most drugs in the clinic today are either small, moderately polar organic molecules or therapeutic proteins; these latter will most often be antibodies. Only about 25% of the proteins in the human genome are (or are thought likely to be) amenable to modulation by one of these molecular classes, and these proteins are termed 'druggable'. Perhaps surprisingly, most of these are still poorly characterised, and an even larger majority are not yet targeted by clinically useful drugs. Platforms that integrate chemical and genomic information together can aid both target and lead compound selection.

Recently, genomics-based technologies are allowing scientists to start looking for drugs outside these broad categories. The CRISPR/Cas system is a form of DNA-based 'gene editing' found naturally in prokaryotes that can be exploited to alter gene sequences quickly and efficiently and thus, potentially, to correct mutations in some of the 3,000 human genes that have been linked to disease. Ethical issues and safety questions aside, the 'disruptive potential' for this technology in healthcare is without doubt immense.

Genomics in Drug Development

It is self-evident that efficacy alone will not make a molecule into a successful drug. The role of genomics and allied technologies in the development stage – in predicting pharmacokinetics, toxicity and drug-drug interactions, is not as obvious as it is in target and lead selection, but it is no less important. Collaboration is also playing a key role here, as exemplified in different ways by CDISC, a charitable organisation developing international data standards to support clinical research and regulatory submission, and AstraZeneca's DREAM project investigating drug-drug interactions. That involved 'crowd-sourcing' predictions of drug-drug combinations that might have a synergistic effect on a given cell type and therefore disease. Like so many of the initiatives discussed during the meeting, DREAM required the company to open some of its 'silos' and to release compounds and data into the public domain.

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