Meeting Report

Drug discovery in the wake of genomics

Suzanne Berry

The Impact of Genomics on Drug Discovery and Development Keystone meeting was held at Santa Fe, New Mexico, USA, 2–7 February 2001 and was organized by Brian Metcalf, Paul A. Bartlett and Elliot Sigal.

In the wake of genomics, a colossal amount of information has hit the field of drug discovery. The flood of potential drug targets requiring investigation, as well as vast amounts of other information from genomics projects, has left the drug discovery process in disarray. To cope with this, there have been numerous changes and advances in target validation strategies, as well as the development of high-throughput screening technologies. The need to analyse the mass of data has led to many technological advances in bio- and chemi-informatics and the impacts of previously intangible concepts, such as pharmacogenomics and pharmacogenetics, are now being realised. Pre-clinical development approaches have also had to be updated, as have methods for safety and toxicology testing and the determination of drug metabolism. In addition, as more and more patent applications are being made, both for the technologies and for potential drugs and targets, patenting policies have been left behind and need to be updated. This conference examined the impact of genomics on drug discovery, including new technology, intellectual property rights and bioinformatics.

The conference included (1) functional genomics and target validation; (2) the impact of new technologies on drug discovery; (3) what is new in pre-clinical drug selection? (4) pharmacogenomics in practice; (5) intellectual property issues; and (6) the interface of information technologies and life sciences.

Functional genomics and target validation

The challenge is to get from the number of genes that we have discovered, via functional genomics, to targets and also to find genes by looking at homologs to existing targets. Christine DeBouch (SmithKline Beecham Pharmaceuticals, PA, USA) described how genomics can be applied to the identification and validation of novel targets for drug discovery. DeBouch emphasized that genomics should not be thought of in isolation, it should be used alongside other disciplines by different types of institutions to tackle drug discovery as a multidisciplinary enterprise. She stressed that comparative genomics is vital and that advances need to be made across all technologies and research fields to obtain the whole picture about what is going on in cells and organisms before the full potential of genomics will be realized. However, genomics is already proving its worth, SmithKline Beecham has studied the role of cathepsin K in osteoporosis; a lead compound is now in preclinical development and has demonstrated efficacy after oral dosing in animal models of bone resorption.

The methods that are now being used to process the information provided by genomics are way beyond the previous boundaries of our data-processing capabilities. Many argue the relative merits of studying the transcriptome rather than the proteome but what is important is not the source of information but what you do with it. Stephen Friend (Rosetta Inpharmatics Inc., Kirkland, WA, USA) explained that we have got used to target-centric methods of drug discovery and development and should be moving away from that strategy. One in five drugs on the market was developed for something other than what it is now being used for, and thus a lot of useful information gathered when the drug is being researched is discarded because it isn't relevant to the role intended for the drug. We should obtain the whole picture about what is going on before matching end roles for drug targets and should use 'cell reporters' to obtain a high resolution picture of what is happening in the cell. Rosetta Pharminformatics has developed several core informatics technologies to this end. Friend believes that if the genome is used as a sensor pad and experiments are thought of as data to add to a pool of information that can be used later, we will make significant progress in the field of drug discovery.

Recent years have shown major development in high-throughput technologies. James Pigott (Lexicon Genetics, The Woodlands, TX, USA) described how Lexicon Genetics now analyses mice at an unprecedented rate using high-throughput phenotypic analyses and that the challenge now lies in data mining. The company creates 3000 clones per week and hopes to have sequenced the mouse by the end of the year. Usually, a full study of knockout mice takes approximately three years but Lexicon uses recently developed mouse-scale clinical technologies to dramatically speed up the process. The system is robust, non-invasive, amenable to digital data capture in a relational database and longitudinal (i.e. non-lethal). Pigott also believes that a greater understanding of real biology and physiology will lead to better use of genomics.

Impact of new technologies on drug discovery

Technologies in proteomics mostly involve physical disassembly and include 2D electrophoresis, prefractionnation, mass spectrometry, bioinformatics, protein expression and antibody generation. Fractionation is the key to marker discovery in the human serum proteome.

John Houston (Bristol Myers Squibb, Wallingford, CT, USA) discussed ultra high-throughput screening at Bristol Myers Squibb. He described how we now need increased quality and success rates and to develop predictive databases so that informed decision making can be part of the R&D process. Initiatives to drive down the costs of R&D, such as outsourcing, automation and miniaturization, enable high throughput and the targeting of new bottlenecks.

Structural genomics has an important role in drug discovery because it enhances understanding of molecular events in biological processes. Patricia Weber (Schering Plough Research Institute, Kenilworth, NJ, USA) has been studying the enzymes of hepatitis C virus (HCV) with the hope of developing a drug to inhibit replication. If the structure of

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RNA-dependent RNA polymerase is determined, study of the active site can provide a template for a drug and because the RNA-dependent RNA polymerase of HCV has a globular structure rather than the typical structure, any drug directed against it is potentially specific.

What is new in preclinical drug selection?

Gordon Ringold (SurroMed Inc., Palo Alto, CA, USA) enthralled delegates with his presentation about novel phenotyping technologies for target identification and biomarker discovery. SurroMed has taken multiplexing and miniaturization to an unprecedented level. The Nanobarcode™ (NBC) is used as a bead on which to perform chemistry and has the advantage over polystyrene beads that there is less 'noise' and non-specific binding is low. NBCs are freestanding cylindrically shaped metal nanoparticles, the composition of which varies along their length. Any chemistry can be put on the surface of the molecules. The company has developed methods for reading and identifying NBC images and interfaces the use of NBCs and mass spectroscopies.

Sohaila Rastan (Ceros Ltd, Cambridge, UK) urged delegates to think of yeast as a test tube and *Caenorhabditis*, not as a tube under hydrostatic pressure, but as a mini-human in disguise. She said that one of the bottlenecks of drug discovery will always be in biology. The core protein pathways are run by the same number of proteins in different organisms so model organisms are studied and connections between them exploited to pick targets. To this end, the ENU (ethylnitrosurea) mutagenesis programme (see http://www.mgu.har.mrc.ac.uk) has been set up to identify new phenotypes relevant to human disease.

Pharmacogenomics in practice and the regulatory position

Today we prescribe drugs basically by trial and error, which is not cost effective and all medicines are not safe and/or effective in all patients. A pharmacogenetics approach is the answer. Michael Kauffman (Millennium Pharmaceuticals, Cambridge, MA, USA) predicts that diseases will be reclassified on the basis of biomechanisms and molecular markers and that individuals will receive medicine tailored to their molecular profile. For clinical trials to be fully useful in developing drugs for subsets of the population, we need to understand molecular markers so that the right people can be included in trials. However, Cheryl Anderson (Bristol Myers Squibb, Wallingford, CT, USA) explained that such preselection might prove to be inadequate to support regulatory approval for the patient subpopulation that responds to the drug. There are concerns that preselection will be performed without sound rationale for a targeted patient population. Anderson said that we still have a long way to go before the regulatory bodies will include pharmacogenomics information in approval criteria. 'We are always kind of behind the times. There is no other way to do it in such a complex and rapidly evolving field' (FDA Advisory Committee 1999).

The interface of information technologies

Many people described the need for all-encompassing, multidisciplinary, fully relational database and many have started to construct their own versions. John Couch (Double Twist, Oakland, CA, USA) described Double Twist as the only neutral aggregator of genomics databases and analytical tools for advances in gene-based research, medicine and diagnostics. Double Twist integrates information from many collaborators and includes genomic, patent, disease and literature data from the public and propriataries; it also includes links to research-product sites.

Conclusion

Genomics can potentially lead to better clinical candidates, fewer clinical failures, faster drug development and breakthrough medicine. Some believe that it is already delivering these promises, others think that we have a long way to go and that we shouldn't jump the gun by belittling the need to continue trying to understand key processes that we have not yet mastered. In general, it would be fair to say that in the field of protein therapeutics genomics has already impacted the pipeline and in the field of small molecules, early evidence of impact is emerging. The conference provided an excellent forum for debate and a chance to discover how people are already using genomics in drug discovery processes.

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The Integrated Bioinformatics: High-Throughput Interpretation of Pathways and Biology conference was held at Zurich, 24–26 January 2001.

It is a platitude following the joint publication of the sequence of the human genome[1,2], to say that we are at the beginning rather than the end of understanding mechanistic biology. The exponential accumulation of sequence information both from humans and from lower order species is just the tip of the data iceberg. Cataloguing the vast amount of polymorphism within the genome, at least in humans, is well underway by the single nucleotide polymorphism (SNP) consortium. The study of the transcriptome is also underway with the study of the infinitely more complex proteome in its infancy, still reliant on methods that are relatively low throughput and labour intensive. The collation, storage, interspecies comparisons and interpretation of these vast oceans of data were the subjects of this meeting and each issue was covered within its own session.

As a geneticist rather than a bioinformaticion I am an interested party