Post-genomic technologies – thinking beyond the hype

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'In the task of "de-bottlenecking" drug discovery, technology developments will provide clever tools but not magic wands.'

The completion of a high-quality, comprehensive sequence of the human genome, in this fiftieth anniversary year of the discovery of the double helical structure of DNA, is a landmark event. The genomic era is now a reality [1]. Undoubtedly, our scientific understanding of human biology is being transformed, with profound impacts on medical research, practice and business. Alongside this, rapid developments in research technologies, such as high throughput molecular profiling and bioinformatics, are delivering unprecedented amounts of data on parallel measurements of gene and protein content and activity.

However, there has been much hype surrounding the areas of genomics, proteomics and post-genomic medicine. This new science and technology is often promoted over-enthusiastically, with the fundamental impacts failing to materialise within the promised timescales.

New drugs from microarrays?

The past decade has seen heavy investment in gene expression microarray technology for drug discovery, dominated by the Affymetrix GeneChip™. Such platforms enable researchers to profile samples in hugely parallel experiments, accelerating the rate and scope of discovery research. However, concerns about productivity in R&D add further pressure to perform, and in this context, returns from these technologies seem disappointing. Have biochip investments failed to deliver?

The answer is yes. And no. Clearly, the anticipated flood of new drugs has not yet materialised. Yet, to many, this comes as no surprise.

Use of this tool generates more information, rather than less, which is clearly useful in the divergent components of the drug discovery pipeline and, in experienced hands, this technology will deliver a profoundly deeper understanding of genetic function in disease, hence, the number of new potential targets identified has soared. At this level, DNA chip technology has successfully delivered.

But if used injudiciously, these powerful technologies can generate more work for the selective stages of filtering down targets and compounds. The trick in running an effective drug discovery pipeline has always been 'fail quickly' – if you aren't careful, biochips can generate more targets to be assessed and increase the pressure for a harsher triage.

Return on bioinformatics?

A similar story can be told about the rise of bioinformatics, driven by the need to store and analyze the huge volumes of data arising from genomic sequencing, biochips and similar information-intensive techniques. Massive investments have been made throughout the drug discovery world in computing infrastructure and development of sophisticated software applications.

However, one key challenge remains if the full value of these investments is to be realised: data integration is crucial to achieving the true benefits of *in silico* science, and this process is hampered by a lack of established standards and by poor integration tools. This cannot be understated – the next big wave in bioinformatics will be the computational application of 'systems biology' to the drug discovery pipeline. Here, the analysis of multiple components in a complex system can quickly become a computationally intractable task. It is now starting to be acknowledged that the integration of prior knowledge and contextual information will be an essential step toward developing predictive 'systems' models.

Beware proteomics

Proteomics today is being sold on the basis of delivering more drugs – faster and cheaper. Will we also be disappointed by these investments in the future?

The main danger in the excitement for this particular 'next big thing' is that of overlooking the limited capability of the technology. Unlike gene expression technologies, where whole genome coverage on a single assay is now

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effectively achieved, the ability to profile samples across the complete proteome is a long way off. Current techniques developed from traditional protein analysis approaches can only assess a fraction of the proteome space (1–2000 components), and so will never be able to deliver the broad spectrum of benefits that are often assumed.

The proteome represents greater complexity than the transcriptome (by several orders of magnitude; >500,000 components). The key bottlenecks are sample preparation, resolution and quantification – all non-trivial problems. Ironically, microarray technology offers one potential solution to this problem but protein chip technology still requires considerable investment in many areas, particularly in quality reagent development; we should avoid being too optimistic.

Caveat emptor

There has been much hype surrounding the technologies for post-genomic medicine, which have often been promoted over-enthusiastically and with the benefits failing to materialise within the promised timescales. Nevertheless, it is clear that, over time, this revolution will dramatically change our understanding of how drugs and other medical products can be developed and any biopharma company that ignores this area will be left behind. This poses a tricky dilemma for those making further investments in new technology – will the investment pay back?

The motto here should be 'buyer beware'; new approaches must be critically assessed, with a clear understanding of their benefits to the task in hand. In the task of 'de-bottlenecking' drug discovery, technology developments will provide clever tools but not magic wands. And there is always the danger of being seduced by the 'glamour' of being an early adopter of cutting-edge technology.

The problem is often one of setting reasonable expectations; microarrays were never going to produce new drugs overnight, but some believed in and invested in the technologies on this basis. Surely it is the buyer who holds responsibility for critically assessing and clearly understanding the potential business impact of these investments? These technologies are transforming the drug discovery process, therefore they certainly warrant investment, but this should be considered in the context of the right expectations.

Think differently

Highlighting the need to think smarter about how these technologies are used is worthwhile. These technologies provide incredibly powerful research methods but they are not yet robust and are still expensive. Clever tools can be tricky to use and, thus, it is not surprising that it is taking time for the full intellectual contribution of these approaches to demonstrate return on investment.

Indeed, it is also important to realise that, on a higher level, these technologies turn the traditional approach to discovery on its head. Beyond the usual hypothesis-driven reductionist perspective, the ability to explore genome and proteome-wide molecular patterns opens up the opportunity to take a more holistic, data-driven and quantitative view. A change in mind-set is required to fully understand the impact of this paradigm shift.

Beyond the hype, judiciously applied post-genomic technologies are transforming the world of drug discovery, but the realisation that post-genomic technologies demand new ways of thinking about biomedical research is perhaps the most important technology development of all.

References

1 Collins, F.S. *et al.* (2003) A vision for the future of genomic research. *Nature* 422, 835–847

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