Biotechnology and cardiovascular medicine – a hazy past and bright future?

From such successful beginnings, the biotechnology sector has since gone on to have a rather hazy past, for which there are many plausible explanations.

In March 2000, the sector was grossly overvalued and, since then, investors' aversion to the area has flourished due to the perceived risk they felt they were taking. This has led to the growth of many biotechnology companies being stunted since access to capital has become more difficult – studies, especially long-term survival trials in cardiovascular medicine, are a major drain on funds. Without traditional backing from big pharmaceutical companies – colloquially known as 'big pharma' – it is very difficult to bring products to the market.

Another possible reason for the sector's poor stock market performance is that the 'promise' of biotechnology to revolutionise medicine has diminished. The initial optimism surrounding the human genome project is one example. Like many big scientific discoveries in the past, it raised more questions than it answered due to the vast quantity of new genetic data available. Both the biotechnology and the pharmaceutical industries must now: firstly, determine the function of each of the estimated 140,000 human genes; secondly, identify possible candidate drug targets (target discovery); and thirdly, determine a target's therapeutic value (target validation).

There are also too many companies in this area, each with too few molecules in any state of development that merit mentioning, all chasing early partnering deals and Initial Public Offering* (IPO) to try and raise much needed capital.

Clarity could be obtained if scientists/academia unlocked the potential value of their discoveries by 'uncapping appropriate communication of scientific knowledge' to commercial suitors, earlier rather than later. This would improve the chances of biotechnology companies securing the necessary deals and obtaining capital. Appropriate scientific communication interlinked with science is key.

It appears that licensing and partnering deals gain importance, not simply for the revenues they bring, but also for any suggestion to the outside world that independent scientists from large 'pharma' companies endorse the concept. It is not always money that drives deals. Deals are driven by new and unique technologies amongst people who have similar objectives. But these deals often fail because scientists, passionate about their technology, find it difficult to hand over their projects to middle-aged scientific administrators in 'big pharma' and then trust the company to produce a product. Similarly, many 'big pharma' managers can be reluctant to trust research from small organisations or academia.

The future

So what does the future hold? There may well be a mid-term productivity gap, caused by poor target validation in traditional high throughput screening (HTS) systems. Single reporter cell-based systems, which are currently established in 'big pharma' companies, use mostly xenopus oocytes. These model neither a tissue- nor a disease-specific target related in any way to human (patho-) physiology. Target validation in either transgenic or knockout animals is both costly and has very low throughput – it also cannot predict all human side effects or toxicity issues. It is applicable only in later stages of drug development due to time and cost, similar to testing in classical pathology mimicking animal models. This situation could increasingly lead to drug candidates being identified from poorly validated and characterised targets, which might fail late in clinical testing. This could reduce output and, in parallel, increase both the cost and time of developing new drugs.

'In silico' drug screening

There is an urgent need to improve target validation and thus to reduce the risk of bringing forward the wrong drug candidates. One 'bright' area to improve this situation is bioinformatics – a mix of genomics and computing – which it is hoped will reduce both the cost of bringing drugs to market and the time to reach the market by approximately two years. This 'in silico' drug screening will allow scientists to diagnose and predict earlier which compounds work best for specific genetic diseases such as cancer, heart disease and diabetes. It could also revolutionise the way drugs are developed to combat ailments. In addition, microarrays and 'in silico' testing will become important for both metabolic and toxicological screening. It must be stressed that clinical trials will never be

*IPO is a term used to describe the legal and financial processes in which certain types of companies, usually an entrepreneurial business venture and, more commonly, high technology new ventures, are able to sell their shares to the public and hence raise capital by gaining a listing on one of the world's financial markets.

replaced, regardless of the technology. But as our knowledge about genotyping rapidly increases, clinical trials will be able to be designed more efficiently by including this technique in patient recruitment and inclusion criteria from the very beginning of modern drug development.

Diagnostics will also gain importance in time since they will assist in defining both the disease and the likelihood of its successful treatment, even for established therapies. For example, prior to initiating antihypertensive treatment with ACE (angiotensin-converting enzyme) inhibitors, it will be possible to determine whether a patient is likely to be a responder, rather than practising the current 'trial-and-error' principle.

New target validation techniques

Several biotechnology companies are currently focusing on trying to offer better target validation techniques, which should, ultimately, lead to improved predictive HTS tools. As an example, Cardion, a biopharmaceutical company which is actively involved in the field of cardiovascular disease, feels positive about the future due to its ability to provide an unique operating system for drug discovery. This has the potential to overcome problems in target definition and, thus, in drug screening and profiling.

A stem cell-based technology utilises functional genomics approaches in rational target validation and drug design. It provides functional identification, characterisation and validation of candidate genes. Novel tissue- and, possibly, even disease-specific drug screening tools are generated. This means it should be possible not only to find new, validated targets for cardiovascular disease states, but also for virtually all other unmet medical needs independent of the organ(s) involved. By first analysing a population of differentiated cells for gain or loss of functional properties in comparison to a control population without the transfected candidate gene, the target is validated. If reproducible and well characterised (human) cell populations, differentiated from stem cells in sufficient numbers and carrying a reporter gene under the control of the candidate gene promoter, will allow HTS, then only relevant hits will be produced.

A similar approach could be employed for toxicological and metabolic screening of drug candidates in relevant cell lineages generated from stem cells. This will help identify unwanted side effects of compounds and thus save animal experiments, time and the unpleasant recognition of unwanted effects as late as clinical trial phases I and II. With the help of enabler technologies combined with bioinformatics, it will be possible, within the next few years, to shift the peak attrition rate in drug development – currently at the end of phase I – far back in the pre-clinical phase saving years of development time and millions of dollars per compound failure.

We still have much to learn. But a picture is emerging – not least in the treatment of cardiovascular disease states where target- and tissue-specific drug screening and development will be able to improve the positive effect of drugs on the respective disease states. This will allow patients to be treated not purely symptomatically for the first time. Against this background, it is anticipated that the growth of well-positioned biopharmaceutical companies will take off from 2005 onwards and be explosive between 2010–2020. It is important, however, not to forget that this industry is only 25 years 'young' and has expanded well. In fact, with regards to size, the entire US biotechnology industry is still only around twice the size of the US pharmaceutical company Merck.

Thus, for the whole biotechnology industry, the future may well just be at the beginning.

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