Molecular genetics: the Emperor's clothes of drug discovery?

'… the genome sequence has a far greater capacity to mislead than it has to illuminate…'

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In a recent interview published in *Drug Discovery Today* [1], the molecular geneticist Peter Goodfellow outlined his belief that knowledge of the human genome sequence, when harnessed to automated high-throughput technologies, will result in drugs being made more easily. With the continuing decline in the productivity of pharmaceutical R&D, this view is now being challenged from a number of quarters. It has been assumed that studying the genome at a molecular level will reveal new targets for drug intervention and that molecular biology will provide the relevant tools for identifying new drugs. The surprisingly poor success rate of this approach suggests that these assumptions should be questioned.

How useful is the genome sequence in revealing novel therapeutic targets?

We now know that the human genome stands out in having an exceptionally high number of pseudogenes that encode large families of redundant proteins [2]. This indicates that the genome sequence has a far greater capacity to mislead than it has to illuminate; sequence data alone is high-volume, low-quality information. In disease, the importance of a target can only be expressed in terms of functionality, but functional annotation that is based on a genomic sequence is not easy. The best evidence for the role of a new receptor is the observation of an agonist activity in relevant tissues that cannot be accounted for by a known receptor. The existence of a gene, or even the expression of a protein, does not necessarily establish functionality.

Today, the use of cloned recombinant molecules as targets to screen libraries of compounds is common practice. The aim is to reduce the experimental system to the minimum requirements necessary for the study of discreet molecular interactions. However, there is no guarantee that recombinant molecules adopt the relevant structural configuration in isolation and no certainty that agonist or antagonist binding will occur as it does *in situ*. Together with this desire to study molecules in isolation, there is the belief that 'optimum' interactions can be defined. What is usually meant by 'optimisation' is 'maximisation'. The assumption that the best new medicines will be the most potent and most selective against a particular target betrays a misunderstanding of how drugs work. Some of the most successful medicines are remarkably weak or non-selective. For example, aspirin, ibuprofen and cimetidine are blockbuster drugs with potencies in the μmolar range. Drugs such as fluticasone and budenoside, which are widely used to treat asthma, belong to a class of anti-inflammatory steroids that are so non-selective that nobody is quite sure how they work. In the HTS regimes of today, these drugs would not even be rated as 'hits'.

Are genetically engineered cells valid models of disease?

Molecular biologists have also provided us with modified cell lines. Simply, these are dividing cells, which are often derived from the culture of tumours, that have been genetically engineered to enable the study of cell processes or pathways. The elegance of these techniques is seductive – so much so that I believe they are taken too readily as valid models of disease for evaluating drugs. Indeed, many of these genetically engineered cells are grotesque artefacts of life. I find it difficult to believe that their responses can resemble naturally occurring processes. It is ironic that the modern cellular biologist, with his weird collection of mutated cells, is often among the first to question the validity of conventional animal models. Similarly, the increasing use of gene 'knock-outs' seems to be an approach that is highly vulnerable to the creation of misleading artefacts.

Molecular biology as we know it today has emerged from the discipline of physical chemistry not from medical research. The famous publication by Watson and Crick [3] that proposed a structure for DNA comprised results from research performed at the Cavendish Laboratory, which is an integral part of the Department of Physics at the

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University of Cambridge (http://www.cam.ac.uk). To the physicist, a structure is either correct or erroneous and a sequence is either in the right order or incorrect order. There is no question that if an experiment is performed numerous times, several different, yet legitimate, answers can be produced. This attitude is a long way from understanding the principles of variation in biological response as exemplified by John Trevan in the 1920s [4]. Trevan noticed a substantial variation in the response of animals to insulin and he developed a statistical method for analysing biological data that went on to become the basis of experimental pharmacology. Molecular biologists are extremely uncomfortable with tissue or whole animal responses; molecular biologists are unfamiliar with studying fluid, living systems that rely on a complex balance of interrelated mechanisms, which is a process that physiologists and physicians know as 'homeostasis'. When a pharmacologist investigates the effects of selective agents in living tissues, it is like using a fine screwdriver to tune a running motor. These experiments generate low-volume, high-quality information. At present, biological literature is dominated by illustrations that include the gels and blots generated by molecular biologists that convey little feeling for the actions and interactions in living organisms.

I believe that the reductionist, structure-based approach of molecular biology is a poor starting place for drug discovery. However, it has been said that established methods for discovering drugs have run their course. I do not believe this is so. The industry would do well to have a close look at how a major new class of drugs, the anticytokines, was recently discovered. In a clinical research laboratory at the Kennedy Institute (http://www.arc.org.uk/research/kennedy), Ravinda 'Tiny' Maini and his colleagues conducted a straightforward, but illuminating, experiment. They extracted some inflamed tissues from patients suffering from rheumatoid arthritis (RA) and recorded changes in response to particular stimuli [5]. Based on investigations using a neutralising antibody, Maini and co-workers concluded that tumour necrosis factor (TNF), which is a cytokine, plays a pivotal role in arthritis. Additional research indicated that anti-TNF antibodies reduced arthritis in animals [6]. Furthermore, in collaboration with Centocor (http://www.centocor.com), the Kennedy team showed that anti-TNF (infliximab) produced striking therapeutic benefits in patients suffering from RA [7]. The seminal experiment was conducted in 1989 [5] and the drug was launched in 1998 – there were less than ten years between the start of basic research and the product reaching the market and not a trace of high-throughput automation in the whole process. Today, the annual sales of infliximab have topped US$1 billion.

Should greater emphasis be placed on clinical and primary cell investigations?

Cytokines like TNF (cachectin) and interleukin-1 (catabolin) were identified as 'factors' that switch on the destructive processes in arthritic joints [8]. The experiments performed at the Kennedy Institute are the direct descendents of this deductive approach to unravelling disease mechanisms. Furthermore, the discovery of the importance of cytokines in inflammatory disease did not depend upon knowledge of the genes that encode their production. The use of antibodies has been of crucial importance, but again it is questionable how much this has depended upon genomic technologies. The history of antibody use in biological research and in medicine stretches back long before the genomic era. However, the technique that was developed by Cesar Milstein for the production of monoclonal antibodies [9] is central to the development of drugs like infliximab, and yet again it was an academic laboratory that made the discovery. Although a purified anti-TNF antiserum would produce therapeutic effects, the ability to produce monoclonal antibodies overcomes a number of problems. Fusion of antibody-producing cells with tumour cells creates an immortal 'hybridoma' that can be cultured indefinitely to provide a source of high-affinity antibody. Here, cell biology comes into its own; not by modelling disease processes, but as an enabling technology.

Infliximab is a chimeric molecule that is made up from mouse and human protein and the molecular biologists have been quick to point out that this relatively crude antibody can be improved upon. However, a number of highly sophisticated genetically engineered, fully humanised follow-ups to infliximab have failed to show an overall improvement and some are significantly less active. It seems that the genetic engineers have some way to go before they can compete with the 'optimisation' processes of the mouse immune system.

Although there are elaborate *post hoc* explanations of how the anticytokine biopharmaceuticals were developed, the fact remains that the Kennedy group took diseased tissue from ill people, performed some neat experiments and subsequently proved their theory using a relatively low-tech antibody in patients. We owe the discovery of the therapeutic value of anti-TNF antibodies to biological scientists who were interested in human disease and who carried out their experiments using relevant systems. Cellular biology and recombinant technologies had their part to play, but in an enabling capacity rather than a discovery role. I say this not to diminish the importance of these techniques but to place them in perspective. And this, I guess, is my underlying argument. Reading Peter Goodfellow's vision of automated innovation [1], I feel

that the industry has got the 'new biology' out of perspective, and this has been at the expense of scientific approaches that remain essential for drug discovery.

Where to now?

It appears that the pharmaceutical industry has become a victim of the success that it achieved in the mid-20th century. The massive and prolonged profitability of the industry has led to complacency whereby the principles of applied industrial science have been forgotten. The infatuation with new biology and molecular genetics has not maintained the flow of new products. The large pharmaceutical companies are increasingly dependent on old products that have a rapidly expiring patent-life. Alarmingly, the direction of discovery research is often governed by scientists who are unfamiliar with the origin of these drugs. The industry needs to rediscover the discipline of deductive pharmacology. Above all, it needs to promote clinical pharmacology, which is a speciality that has historically been the poor relation in the National Health Service (UK; http://www.nhs.uk).

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