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EDITORIAL

Drug Discovery: Myth and Reality

An editor penning an editorial column has a wonderful advantage; the hurdles of referees and sub-editors do not stand as obstacles before the article is published. For a regular columnist, the most difficult task is to find a topic to write about. Then comes the almost equally formidable task of gathering at least a smattering of facts. Finally, there is the threatening spectre of the deadline for the printers. Committed, as I am, to writing a fortnightly column for this journal, I am often rescued in the difficult task of finding a subject, by papers sent to me by friends, colleagues and, most importantly, readers whom I have never met. A few days ago a friend sent me a marvellously provocative editorial by Gerry Higgs in *Drug Discovery Today* (2004, **9**, 727). The polemic entitled 'Molecular Genetics: the Emperor's Clothes of Drug Discovery' was a frontal attack on the prevailing view 'that knowledge of the human genome sequence when harnessed to automated high-throughput technologies will result in drugs being made more easily'. Higgs was challenging a view expressed in the same journal by Peter Goodfellow, an academic geneticist-turned-manager of drug research at GlaxoSmithKline (*Drug Discovery Today*, 2003, **8**, 1017). Goodfellow presents an extremely optimistic view of the impact of high throughput screens (HTS) and high throughput (HT) chemistry, on the traditionally slow process of drug discovery. The drug discovery cycle is the process where a promising laboratory finding is converted into a marketable product; an uncertain process that resembles a game of snakes and ladders, potential products often failing in the final stages of clinical trials. The timescales involved are immensely long, estimates of 10–15 years being common. Indeed, the gulf between the laboratory and the clinic can be formidable. The mainstays of the conventional drug industry have been medicinal chemistry and microbiology. While the chemists have toiled ceaselessly producing molecules, structures patiently modified in incremental fashion, the microbiologists have provided both antimicrobial screens and an inexhaustible supply of culture filtrates, which provide a treasure trove of new molecules. The history of antibiotic research is replete with wonderful molecules that emerged from microbial cultures, penicillin, streptomycin, tetracycline and erythromycin among them. Once 'leads' have been identified, the task of moving forward requires careful pharmacological and toxicological evaluation, before the clinical trials can begin. But, as the drug industry has matured and as the regulatory controls have become more stringent, the process of discovering promising new molecular entities has become more difficult, more time consuming and significantly more expensive.

Over the last decade or so, the advances in genome sequencing, protein analysis and computational biology have been spectacular, giving rise to the expectation that the new technologies will hasten the process of drug discovery. 'High throughput' is a magical prefix that promises to make chemical analysis and pharmacological screening a matter for robots; raising hopes that automation will indeed aid innovation in the search for new pharmaceuticals. Combinatorial synthesis, a favourite with pharmaceutical R&D managers, coupled with automated high throughput screening has often been touted as the driving technology of future drug discovery. With genes and pharmaceutical targets appearing in profusion, it seemed only a short step to screening tens of thousands of ligands to select new 'lead' molecules. These 'leads' would then be optimized by computational scientists using 'docking' techniques, which would reveal the best fit of low molecular weight ligands to macromolecular receptors. This 'in silico' (an infelicitous phrase) approach would presumably save medicinal chemists years of toil; quickly directing their energies towards producing optimal molecules. The new 'paradigm of drug discovery' has been relentlessly propagated at innumerable conferences and in articles strewn across the sprawling literature of chemistry, biology, medicine and computer science. The biological revolution has spawned many new disciplines, genomics, proteomics, metabolomics, systems biology and bioinformatics. The confluence of these areas is expected to accelerate the drive towards new drugs. Enthusiasts for the new technologies have looked into the future and announced that 'pharmacogenomics', a term that promises customized drugs for individuals, is just around the corner. The rhetoric of drug discovery research has been raised to fever pitch. It is in this context that Higgs' assault on molecular gene-

tics and its role in drug discovery makes interesting reading. Indeed, over the last couple of years even the US Food and Drug Administration (US FDA) notes a fall in the number of new molecules entering the regulatory pipeline. This decline appears at odds with the optimistic projections of the proponents of the new technologies. With the timescales for discovery lengthening and the costs of innovation rising (one estimate that I came across was as high as $ 800 million as the cost for introducing a new drug), the game of mergers and acquisitions has become an integral part of the pharmaceutical industry.

In his essay, Higgs questions the assumption '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 indentifying new drugs. The surprisingly poor success rate of this approach suggests that these assumptions should be questioned' (*Drug Discovery Today*, 2004, **9**, 727). I particularly liked his emphatic dismissal of 'the assumption that the best new medicines will be the most potent and selective against a particular target'. Higgs argues that this view is based on a 'misunderstanding of how drugs work'. He supports his thesis by pointing out that '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 micromolar range'. The reference here is to the hunt for 'nanomolar' receptor ligands, molecules that seek their targets with remarkably high affinities. Higgs drives his point home by pointing out that '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 high throughput screen regimes of today, these drugs would not even be rated as "hits" '. Higgs goes on to question the validity of genetically engineered cells as disease models and argues that gene 'knock outs' are 'highly vulnerable to the creation of misleading artefacts'. In stating 'that the reductionist structure-based approach of molecular biology is a poor starting place for drug discovery', Higgs clearly argues for a greater emphasis on approaches that move forward from clinical investigations. To bolster his case, Higgs cites the case of infliximab, an anti-inflammatory cytokine used for treatment of rheumatoid arthritis, developed over the period 1989–1998. Here the initial leads in seminal work by Ravinder Maini and Marc Feldman at the Kennedy Institute, Imperial College, London came from work with inflamed tissues from patients. Maini and Feldman received the 2003 Lasker Award for this achievement.

The history of drug research over a period of a century, since Paul Ehrlich introduced the concept of chemotherapeutic agents, is a marvellous record of accomplishment. The great victories of the antibiotic era were often serendipitous; penicillin, streptomycin and tetracyclines followed in quick succession. The successes of the 1950s and 1960s were spearheaded by the work of Gertrude Elion and George Hitchings at Burroughs Welcome and James Black at King's College, London, who between them were responsible for developing a large number of drugs, many of which are widely used today. To Elion and Hitchings goes the credit for introducing azathioprine, the first immunosuppressive agent, allopurinol for gout, pyrimethamine for malaria and trimethoprim for bacterial infections. Later, Elion went on to introduce the antiviral, acyclovir using the principle of exploiting differences in nucleic acid metabolism between target and host; an approach that would later be followed in developing the AIDS drug, azidothymidine (AZT). Black used an incisive approach, relying on a deep understanding of physiology, to discover propranolol, the 'beta-blocker' used for heart disease and cimetidine used for treating gastric ulcers. Black, Hitchings and Elion received the 1988 Nobel Prize for Physiology or Medicine; one of the rare instances where drug discovery has been honoured in recent times.

In reading Goodfellow's optimistic view of the future of drug discovery and Higgs' characterization of the new technologies as a case of the 'Emperor's new clothes', I was struck by the evident tensions between the classical disciplines of pharmacology, physiology and medicinal chemistry on one hand and the new offshoots of molecular and cellular biology on the other. Higgs notes that 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'. Ironically, although 'drug discovery' is a widely trumpeted activity, pharmacology is a low-profile discipline with none of the glamour associated with modern biology or medicine. Curiously, in his Nobel lecture, James Black advanced a view on a discipline that he termed as analytical pharmacology: 'What we are allowed to see of a new molecule's properties is totally dependent on the techniques of bioassay that we use. The prismatic qualities of an assay distort our own views in obscure ways and degrees. Our only defence lies in restless improvement in technique and experimental design in the hope that collimation of several techniques will improve the reliability of our vision. We would make changes self-consciously today, but then it was intuition.'

Maybe some of the classical disciplines that have contributed to drug discovery in the past, may well do so again in the future. In drug discovery research today, it is becoming increasingly hard to distinguish between myth and reality.

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