

Editorial

Drug evaluation, drug development and pharmacogenetics: celebrating 30 years of progress

A. Li Wan Po

Centre for Evidence-Based Pharmacotherapy, Aston University, Birmingham, UK

The Journal was launched in 1975. To celebrate 30 years of continuous publication, we thought it would be appropriate to look back on progress made during this period in drug evaluation, drug development and pharmacogenetics, core areas of interest of the Journal.

DRUG DEVELOPMENT AND THE APPLICATION OF SCIENCE

Despite current concerns about whether drug discovery is slowing (1), the last 30 years has seen dramatic progress. Two outstanding technological advances in 1975, contributing to the search for new drugs and better understanding of their modes of action, were the development of monoclonal antibodies (mAB) by Köhler and Milstein (2) and the detection of specific sequences among DNA fragments by Southern (3). The director's dream in Aldous Huxley's 1932 *Brave New World* was to produce clones indefinitely from a single bokanovskified egg (4). Köhler and Milstein achieved this, at least at the cellular level, by hybridization and 'immortalizing' of an antibody-producing cell with a myeloma cell. While the mAB were immediately hailed as the magic bullets sought by Ehrlich (5, 6), it was soon obvious that the development of safe and effective therapeutic or diagnostic mAB would be slow and problematic. Antimouse antibody response, and antigenic modulation, by which cells escape destruction by redistributing and losing antigen-antibody complexes from their surfaces, dampened initial optimism (7, 8). However, persistence led to muromonab-CD3 becoming the first mAB to be licensed for general use in the prevention of rejection of renal transplants.

Correspondence: A. Li Wan Po, Centre for Evidence-Based Pharmacotherapy, Aston University, Birmingham B4 7ET, UK. Tel.: 121 359 3611; fax: 121 359 4693; e-mail: a.liwanpo@aston.ac.uk

Today, there are 30 mAB licensed for treating or diagnosing human disease. These range from abciximab for the prevention of cardiac ischaemic complications, to infliximab for the treatment of rheumatoid arthritis and Crohn's disease and trastuzumab for the treatment of breast cancer associated with over-expression of the HER-2/neu, the epidermal growth factor receptor. The mAB are not the perfect drugs dreamt by Ehrlich. For example, there are concerns about reactivation of tuberculosis and the development of cancer as the immune system is dampened by mAB acting against tumour necrosis factor (TNF), and other anti-TNF agents (9). Tumour resistance, leading to treatment failure, also develops against initially, highly effective mAB. Despite the shortcomings of currently licensed mAB, no one would dispute that the Nobel Prize awarded to Köhler and Milstein in 1984 was well deserved. What is even more impressive is that the mAB technology was never patented by the discoverers, or their employers the UK Medical Research Council. This oversight reputedly earned, those involved, a rebuke from Margaret Thatcher but the scientific community and humanity both undoubtedly became the richer for it (10).

Southern's hybridization method for the detection of fragments of DNA, now known as Southern blotting, provided the insight for the development of other methods for detecting RNA (Northern Blotting) and protein (Western Blotting) fragments and for subsequent innovations such as DNA fingerprinting and genotyping. The profiling of DNA, led to the deciphering of the human genome and publication of the full first draft in 2000 (11, 12).

The year 1975 also saw the award of the Nobel Prize to Renato Dulbecco, David Baltimore, and Howard Temin for discoveries, which made possible the development of biotechnologically

engineered therapeutic proteins such as human insulin and interferon. Dulbecco discovered that viral DNA may integrate itself within the host nuclear DNA (13). Temin extended this work to show that RNA viruses could produce DNA that was subsequently incorporated into the nuclear DNA (14). This ran against the prevailing dogma that DNA led to RNA and thence to proteins. Temin and Baltimore (14, 15) went on to independently demonstrate that this occurred through the intermediary of reverse transcriptase.

Temin and Baltimore's discovery provided the key to overcoming the problem posed by bacteria such as *Escherichia coli*, being unable to deal with introns found in human genes. While it was theoretically possible to chemically synthesize the intron-free gene prior to insertion into the bacterial plasmid, reverse transcriptase provided a much more elegant solution. The post-transcriptionally, edited messenger RNA for the target protein (e.g. human insulin) could be used to generate the complementary DNA (cDNA). This could in turn be incorporated into the plasmid. Transcription within the bacterial cell would then generate the corresponding mRNA for translation to the target protein. This forms the basis of production of most of the currently licensed genetically engineered proteins. Dulbecco, Temin and Baltimore's work also provided the foundation for understanding oncogenic viruses and tumorigenesis.

DRUG REGULATION AND POST-MARKETING SURVEILLANCE

The year 1975 was important from a drug regulatory perspective too with the setting up of the European Committee for Proprietary Medicinal Products. That year witnessed the report of an association between use of practolol and the oculomucocutaneous syndrome, and the drug's withdrawal (16). This new adverse effect made clear that thalidomide was not the only drug with very severe side-effects. The very recent high profile withdrawals of rofecoxib (VIOXX), cerivastatin, mebifradil and non-parenteral vaccines have led to suggestions that all is not well with drug regulation (17). Given that at the time of licensing only a few thousand patients would have been exposed to any new drug, an absence of serious adverse effects should be interpreted with caution and close post-

marketing surveillance is necessary to prevent too many patients being harmed (18). Until many more patients have used a new drug, a marketing licence for it should be viewed as a conditional one. To paraphrase the chairman of the US Federal Reserve Board, Alan Greenspan's comment on the monetary landscape, 'uncertainty is not just an important feature of the drug regulatory landscape; it is the defining characteristic of that landscape' (19). Those who ignore this, do so at their peril, be they patients, prescribers or drug companies. Drug regulators know this only too well but it would appear that they have not had the will and/or the resources to enforce post-marketing surveillance that drug companies undertook to carry out as a condition of the granting of their product licenses.

RESPONSIBLE PRESCRIBING

'I don't understand anything. Nothing. Least of all why you don't take soma...Instead of feeling miserable, you'd be jolly. *So jolly*'. This exhortation by Lenina in the Brave New World has had modern echoes in the marketing and prescribing of benzodiazepines and antidepressants among others. These examples remind us of the need to temper our enthusiasm for drug innovations, lest we end up looking silly... *So silly*.

EVIDENCE-BASED MEDICINE, DRUG EVALUATION AND PHARMACOGENETICS

Despite the great contribution that the evidence-based movement has made to rationality in the practice of medicine, its focus on the randomized controlled trial is now widely accepted to have been too narrow. Organizations such as the Cochrane collaboration are working hard to broaden their perspectives to include observational studies so as to capture the harm that effective drugs could cause the patient.

Current clinical trials and the interpretation of their results still largely concentrate on average effects. Yet therapy is aimed at the individual patient. With greater understanding of pharmacogenetics, it is now possible to personalize therapy for some drugs. There is little doubt that, with the confluence of the statistical sciences, bioinformatics and molecular medicine, this pharmacogenetic revolution will accelerate. While progress

may not be qualitatively as predicted, rapid it certainly will be. Just as with the electronic revolution, the future will not be what it used to be (20). John von Neumann's predictions about 'self-producing automata to build our homes, cook our food, and wait on us at table' have not come true but the Internet and the personal computer have, to change the lives of almost all of us in the developed world.

Just envisioning the possibilities of the new biotechnologies and genetics on the practice of medicine is humbling. While Huxley's 'soma' vision of mind-altering drugs had appeared tantalizingly near with the developments of the anxiolytic and hypnotic benzodiazepines, and the antidepressants, both classes of drugs have led to disappointment after widespread use and misuse. Despite these setbacks, the 'better than Prozac' psychiatric drugs hoped for by Baronides will surely come (21). Haldane, the first person to point out the genetic control of blood groups and of many enzymic reactions, described an ectogenetic world, which is now partly with us with *in vitro* fertilization and pre-implantation diagnosis of genetic diseases. With these advances, the need identified by Haldane for developing an adequate moral and ethical foundation to assimilate the new technologies, way back in 1923, is even more urgent today, given the potential intrusiveness of genetic profiling (22).

Haldane's concern that, 'The tendency of applied science to magnify injustices until they become too intolerable to be borne,' is demonstrated by recent concerns about access to anti-retroviral drugs. Even Jean-Pierre Garnier, the chief executive of GlaxoSmithKline, the company at the centre of recent controversies about the pricing of those drugs had to admit that 'They (the industry) could have jumped on the HIV crisis in Africa much more aggressively. We always end up doing the right things, but sometimes we do it too late' (23). However, as Dyson reminded us, 'the strongest efforts in applied science have been concentrated upon market-driven projects that are expected to lead to...toys for the rich (24). As Garnier said, we need to 'sell our drugs for some profit' to re-invest in expensive research. This reality will always be in conflict with human proclivity to come to the rescue of those most in need.

THE NEXT 30 YEARS

Biotechnological innovations suggest 'a world in which living to a hundred or even beyond will one day be common if not typical' (25, 26). Yet, a paradox is that our lifestyle is leading to more prevalent diseases such as obesity, diabetes, acquired immunodeficiency syndrome (AIDS) and hypertension, which will surely shorten lifespan (27). We have already got used to decreasing life expectancies in some countries ravaged by the AIDS epidemic. Perhaps we shall need to get used to within-country bimodal life expectancy distributions. Alas, better drugs are unlikely to be solutions for this future, increasingly divided world.

SERVING AS AN INTERNATIONAL MULTI-PROFESSIONAL FORUM

When the journal was first published there were visions of the pharmacist with a stethoscope round the neck doing very much what the doctor did, including reading electrocardiograms and X-rays. But it soon became apparent that these scenarios described duplications, which diverted from the expertise of the pharmacist, namely a detailed knowledge of drugs. Clinical did not mean copying what the doctor did but working in collaboration to optimize pharmacotherapy of patients. This realization led to the journal becoming a forum for health professionals on drug therapy. That the journal has succeeded in this role is reflected by the diversity of professional and national backgrounds of the authors of the journal. This current issue draws authors from all four corners of the world.

The focus of the journal highlighted by the sub-headings of this commentary remains. Each issue of the journal in this celebration year will carry invited articles describing the impact of the advances highlighted herein. We would also like to invite contributions focussing on those issues from readers.

REFERENCES

1. National Institute for Health Care Management (2002) *Changing Patterns of Pharmaceutical Innovation*. Washington: NIHCM Foundation.
2. Köhler G, Milstein C (1975) Continuous cultures of fused secreting antibody of defined specificity. *Nature*, **256**, 495–497.

3. Southern EM (1975) Detection of specific sequences among DNA fragments separated by gel electrophoresis. *Journal of Molecular Biology*, **98**, 503–517.
4. Huxley A (1932) *Brave New World*. London: Chatton and Windus Ltd.
5. Schwartz RS (2004) Paul Ehrlich's magic bullet. *New England Journal of Medicine*, **350**, 1079–1080.
6. Ehrlich P (1908) Partial cell functions. Nobel Lecture, 11 December.
7. Miller RALR (1981). Response of cutaneous T cell lymphoma to therapy with hybridoma monoclonal antibody. *Lancet*, **ii**, 226–230.
8. Cobbold SPWH (1984) Therapeutic potential of monovalent monoclonal antibodies. *Nature*, **308**, 460–462.
9. Fleischmann R, Iqbal I, Nanseshwar P, Quinceno A (2002) Safety and efficacy of disease-modifying anti-rheumatic agents. *Drug Safety*, **25**, 173–197.
10. Springer TA (2002) César Milstein (1927–2002). *Science*, **296**, 1253.
11. Lander ESLL, Linton LM, Birren B *et al.* (2001) Initial sequencing and analysis of the human genome. *Nature*, **201**, 860–921.
12. Venter JCAM, Adams LD *et al.* (2001) The sequence of the human genome. *Science*, **291**, 1304–1351.
13. Dulbecco R (1975) From molecular biology of oncogenic DNA viruses to cancer. Nobel Lecture.
14. Temin HM (1975) The DNA provirus hypothesis. Nobel Lecture.
15. Baltimore D (1975) Viruses, polymerases and cancer. Nobel Lecture.
16. Wright P (1975) Untoward effects associated with practolol administration: oculomucocutaneous syndrome. *British Medical Journal*, **1**, 595–598.
17. Topol EJ (2004) Failing the public health – Rofecoxib, Merck, and the FDA. *NEJM*, **351**, 1707–1709.
18. Rumke CL (1975) Implications of the statement: no side effects were observed. *New England Journal of Medicine*, **292**, 372–373.
19. Greenspan A (2003) *Monetary policy under uncertainty*. Washington, DC: The Federal Reserve Board. (<http://www.federalreserve.gov/boarddocs/speeches/2003/20031002/> accessed 17 December 2004).
20. Valéry Paul (1945) *Regards sur le monde actuel*. Paris: Editions Flammarion.
21. Barondes SH (2003) *Better than Prozac*. New York: Oxford University Press.
22. Dronamraju KR (1995) *Haldane's Daedalus Revisited*. Oxford: Oxford University Press.
23. Ashworth J (2004) 'You have got to give our folks the chance to become millionaires'. J-P Garnier Interview. London: The Times, 15 November, 48–49.
24. Dyson F (1995) Daedalus after seventy years. In: Dronamraju KR, ed. *Haldane's Daedalus Revisited*. Oxford University Press.
25. Aaron HJ, Schwartz WB (eds) (2004) *Coping with Methuselah: The Impact of Molecular Biology on Medicine and Society*. Washington: Brooklyn Institution Press.
26. Oeppen J, Vaupel JW (2002). Demography. Broken limits of life expectancy. *Science*, **296**, 1029–1031.
27. Peeters ABJ, Willekens F, Mackenbach JP, Mamun AA, Bonneux L (2003) Obesity in adulthood and its consequences for life expectancy: a life-table analysis. *Annals of Internal Medicine*, **138**, 24–32.