Opinion TRENDS in Biotechnology Vol.22 No.11 November 2004

The myth of the biotech revolution

Paul Nightingale[1] and Paul Martin[2]

[1]Science Policy Research Unit, Freeman Centre, University of Sussex, Brighton, BN1, UK
[2]Institute for the Study of Biorisks and Society (IGBIS) Room B13, Law and Social Sciences Building, University Park, Nottingham, UK, NG7 2RD

The existence of a medicinal 'biotech revolution' has been widely accepted and promoted by academics, consultants, industry and government. This has generated expectations about significant improvements in the drug discovery process, healthcare and economic development that influence a considerable amount of policy-making. Here we present empirical evidence, from a variety of indicators, that shows that a range of outputs have failed to keep pace with increased research and development spending. Rather than producing revolutionary changes, medicinal biotechnology is following a well-established pattern of slow and incremental technology diffusion. Consequently, many expectations are wildly optimistic and over-estimate the speed and extent of the impact of biotechnology, suggesting that the assumptions underpinning much contemporary policymaking need to be rethought.

Over the past decade consultants, policy makers, academics and industrialists have promoted a model of technical change in which biotechnology in general, and genomics in particular, are revolutionizing drug discovery and development ([1–5], http://www.bio.org/er/biotechtools.asp). This 'revolutionary' model has generated widespread expectations that biotechnology has the potential to create an increased number of more-effective drugs and bring about radical changes in healthcare, involving a shift from reactive to preventative and more personalized medicine [6–11, http://www.dh.gov.uk/NewsHome/Speeches/SpeechesList/SpeechesArticle/fs/en?CONTENT_ID=4083803&chk=g/wsdb]. This, in turn, is expected to stimulate a shift in the industrial structure of the pharmaceutical industry from large drug companies to networks of biotechnology firms agglomerated in regional clusters [12–14]. Together these changes are expected to lead to improved health and wealth creation [1,13–16].

These high expectations now underpin much science and technology policy at the OECD [4,5] in the USA [10], the EU [2,13], (http://www.sussex.ac.uk/spru/biotechnology/ebis/), and developing countries (http://www.dst.gov.za/programmes/biodiversity/biotechstrategy.pdf). Agencies at the regional, national and international levels are investing heavily in biotechnology and genomics to establish a foothold in what is seen as a key part of the 'New Economy' [16–19]. Policy takes several forms, including dedicated research funding programmes, fostering knowledge and/or technology transfer, financial and technical support for start-up firms and regional clusters, research and development (R and D) tax credits and lower regulatory hurdles [16–19]. In the UK, the recent report by the Bioscience Innovation and Growth Team (BIGT) argued that to realize the great potential of the molecular biosciences, there is a need for significant change in the relationship between the National Health Service and industry, to allow easier clinical trials, and earlier and cheaper access to new medicines [1]. Similarly, the idea of a biotech revolution has increased policy emphasis on closer networking between university researchers and industry, and focused funding on research that can be directly applied [16].

In this Opinion article we argue that the 'biotech revolution' model of technological change is unsupported by the empirical evidence. Instead, biotechnology is following a well-established, historical pattern of slow and incremental technology diffusion. In making this case, we are not denying that there has been a substantial change in the biological sciences and the organization of R and D within industry. This is obviously happening. However, the translation of this science into new technology is far more difficult, costly and time-consuming than many policy makers believe (see also [20,21]).

Changes in the pharmaceutical innovation process: the evidence

It is possible to measure the impact of biotechnology using indicators of scientific and technological activity such as patents, scientific publications and drug launches. As part of a study funded by the UK Economic and Social Research Council (ESRC), we have analyzed a range of these indicators along the pharmaceutical innovation process. They show that as one moves along the innovation path from basic research to target discovery, target validation, and into clinical development, evidence for a biotechnology revolution rapidly diminishes. Figure 1 shows a sample of our data, generated by Surya Mahdi [22]. This shows the substantial increase in bioscience publications associated with genomics clearly indicating a major, and possibly revolutionary, change in some of the scientific inputs to drug discovery. However, when we move further along the innovation path we observe slow and incremental change. Figure 2 shows the number of therapeutically active compounds patented each year between 1978 and 1998. The bottom line shows the data for the US Patent Office (USPTO) classes 424 and 514 in the period 1978–2002. This is the main patent classification for therapeutically active compounds, and is used as an

Corresponding author: Paul Nightingale (p.nightingale@sussex.ac.uk).

 0167-7799/$ - see front matter doi:10.1016/j.tibtech.2004.09.010

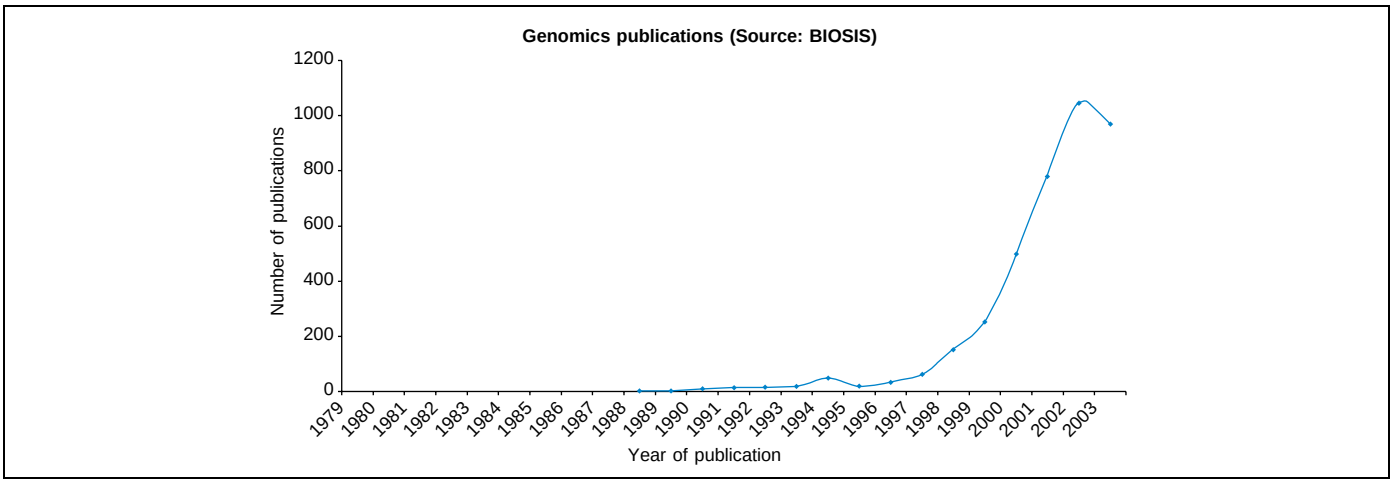

Figure 1. Changes in the number of scientific publications in genomics.

indicator of the number of small molecule compounds considered attractive enough to warrant patent protection, but not necessarily viable enough to enter development.

Although we can see a steady rise in the number of patented compounds, this increase in output needs to be interpreted with care, as it does not take into account substantial increase in research spending or changes in the regulatory environment. Figure 3 shows that during the same period as the approximate seven-fold increase in patenting, R and D spending increased roughly ten-fold. Even if we take into consideration the expected lag of 4–8 years between R and D investments and patenting in these USPTO classes, there is no evidence of dramatic improvement. On the contrary, we find a decline in R and D productivity as measured by the number of patents per dollar of R and D expenditure. Assuming a relatively constant relation between R and D spending, this indicates a possible decline in research productivity, at least in the short term.

This finding needs to be analyzed carefully. Previous historical studies of major technical changes highlight how new technologies typically produce fast, but localized, quantitative improvements in productivity that are highly visible [23]. These are then followed by slow, but often more substantial, qualitative changes that are much more difficult to detect [23]. Early applications of biotechnology involved the pharmaceutical industry picking the 'low hanging fruit'. Today these new technologies are being used to work on more-complex biological problems that were previously too difficult for R and D to address. What the data suggests, therefore, is that any qualitative productivity increases that biotechnology has brought to R and D have not kept pace with the increased complexity of the problems that the pharmaceutical industry and its regulators are now addressing, producing a quantitative decline rather than a revolution.

If we go further on and look at the number of drugs that were actually approved by the FDA in the period 1983–2003, as shown in Figure 4, we see an increase until the mid 1990s, followed by a sharp decline, so that roughly the same number of drugs were approved in 2002 as two decades earlier. When this is set against the substantial increase in R and D expenditure that took place between 1970 and 1992 (i.e. allowing for the 8–12 year lag between research investment and new product launches) there is further evidence of a decrease in productivity, rather than the revolutionary increase we have been told to expect. The peak in the mid-1990s needs to be interpreted within the context of shifting regulatory goal-posts, following the Prescription Drug User Free Act (1992) and the FDA

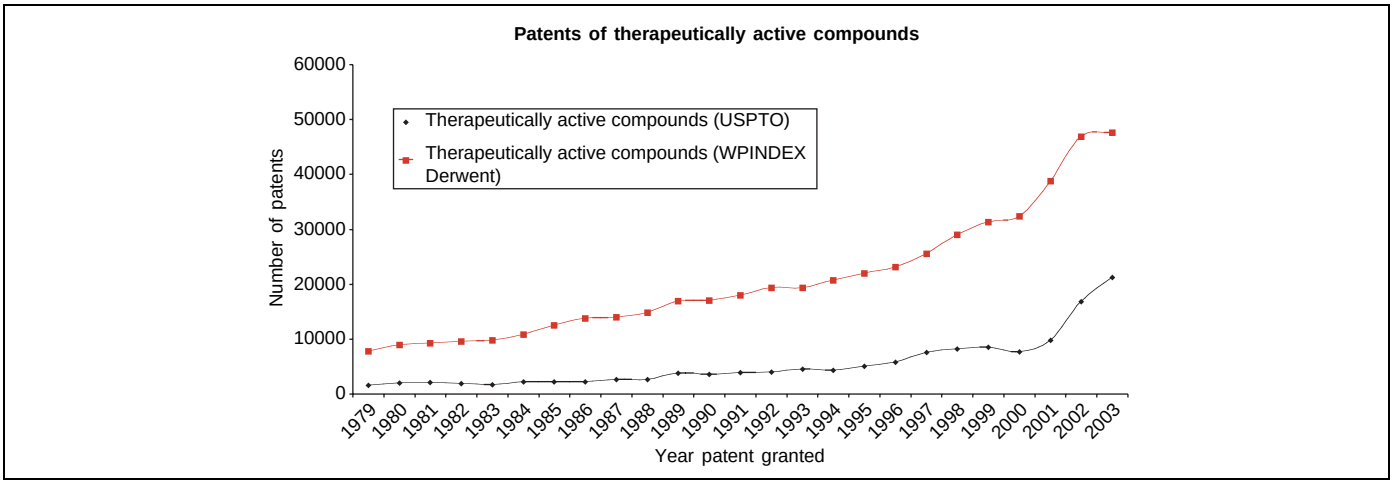

Figure 2. Changes in the number of patents of therapeutically active compounds.

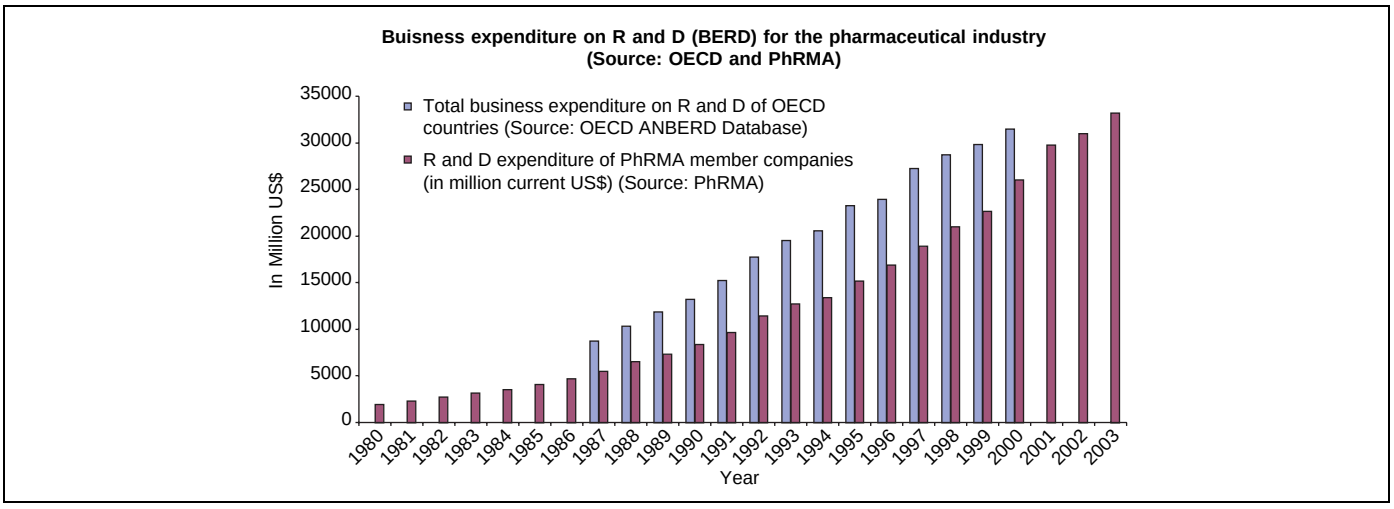

Figure 3. Increases in research and development (R and D) expenditure.

Modernization Act (1997), which allowed accelerated approval and fast track registration. This might be expected to produce a short-term increase in approvals, but such fine-grained analysis is well beyond the limits of this data.

Finally, it is worth examining the number of successful novel biopharmaceuticals that have reached the market since 1980, because these are some of the most tangible fruits of biotechnology. Table 1 gives details of therapeutic proteins and antibodies that sold more than $500m a year in 2002 and 2003 and shows that only 12 recombinant therapeutic proteins and three monoclonal antibodies (MAbs) have become widely used since 1980. Moreover, it is worth noting that three of the therapeutic proteins were already characterized biologicals in 1980 (marked *), with biotechnology simply leading to new production techniques. In other words, the widespread diffusion of recombinant DNA techniques in the 1980s only resulted in a handful of successful new biological drugs. The pattern with MAbs suggests that it can be nearly 25 years before a key scientific innovation becomes effectively translated into new therapies, again suggesting that benefits are hard won. The limited impact of bio-pharmaceuticals on healthcare has recently been highlighted by Arundel and Mintzes [24] using data from Prescrire, which (unlike FDA data) evaluates the performance of new drugs relative to pre-existing treatments. This data suggests that despite huge investments only 16 biopharmaceuticals evaluated between January 1986 and April 2004 were better than 'minimal improvements' over pre-existing treatments. Taken together this empirical evidence provides no support for the notion that there has been a biotechnology revolution.

Understanding what is happening

Several important questions emerge from this analysis. First, why have so many people got their model of technical change wrong? A key factor is the need for innovators and their sponsors to create high expectations to get access to the very considerable resources (money, people, and intellectual property) required to develop new medical technologies. No one is going to invest in a

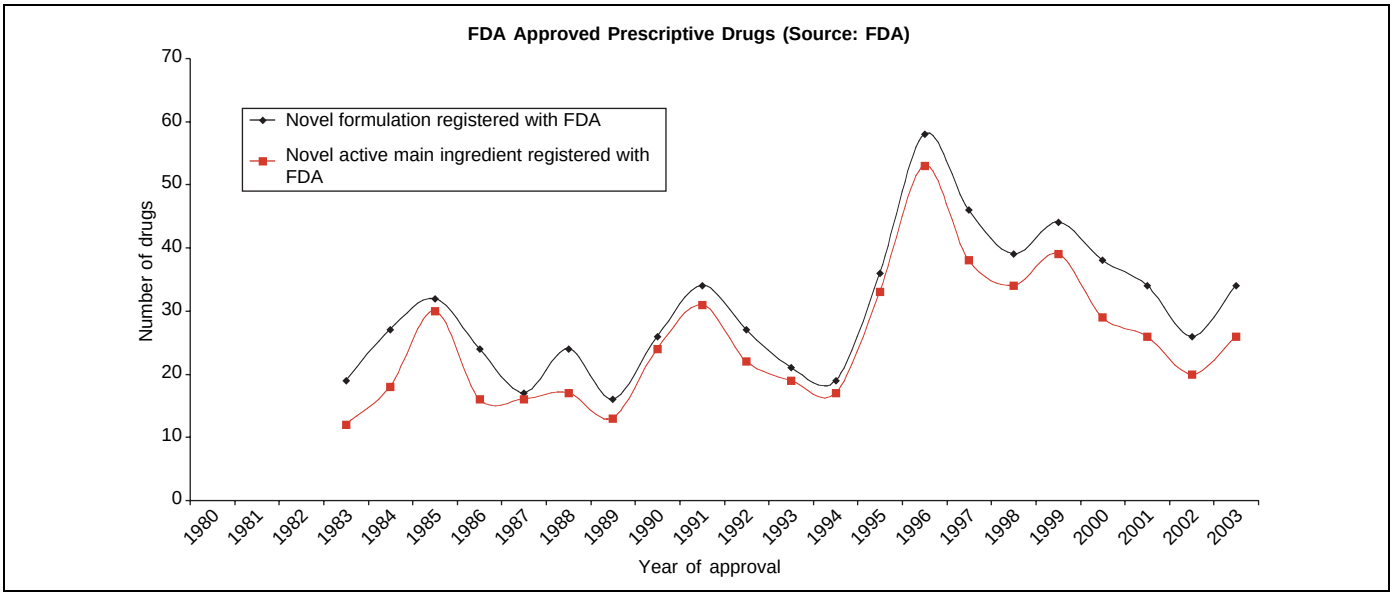

Figure 4. Number of FDA approved prescription drugs 1982–2003.

Table 1. Therapeutic proteins and monoclonal antibodies with sales >$500 million in 2002/2003

Product	First launched by	Annual sales 2002/3 ($m)	Launch date
Recombinant therapeutic proteins			
*Recombinant human Insulin	Lilly	5340	1982 (US)
***Recombinant human growth hormone**	Genentech	1760	1985 (US)
Interferon α	Roche and Schering-Plough	2700	1986 (US)
Erythropoeitin	Amgen/Johnson and Johnson	8880	1989 (US)
Granulocyte-colony stimulating factor	Amgen	2520	1991 (US and EU)
***Blood Factor VIII**	Bayer	670	1992 (US)
Interferon β	Berelex (Schering AG)	2200	1993 (US)
Glucocerebrosidase	Genzyme	740	1994 (US)
Follicle stimulating hormone	Serono and Organon	1000	1995 (EU)
Blood Factor VIIa	Novo Nordisk	630	1996 (EU)
TNF receptor binding protein	Amgen	800	1998 (US)
Lutenising hormone	Serono	590	2000 (EU)
Monoclonal antibodies			
Rituximab	Genentech/IDEC	1490	1997 (US)
Infliximab	Centocor	1730	1998 (US)
Palivizumab	MedImmune	850	1998 (US)

*Already characterized biologicals in 1980.

start-up company, or a large-scale scientific endeavour, such as the Human Genome Project, unless they genuinely believe it has the potential to yield significant returns in a defined timescale. The emergence of the biotechnology industry has rested heavily on the creation of these high hopes and many people in the sector have been active in promoting the idea of a biotech revolution. Management consultants, financial analysts and venture capitalists all clearly have a vested interest in hyping new technologies. Similarly, the promise of a biotechnology revolution provides government policy makers with simple, but as our analysis suggests, probably ineffective ways of promoting regional development, improved healthcare delivery and economic growth. The failure of social scientists is less excusable.

Having said this, it is important to note that not everyone has believed all the hype surrounding biotechnology and genomics [e.g.,20,22,25,26]. Within the pharmaceutical industry, the debate has been far more nuanced and many people have pointed out the mismatch between expectations and reality, and have stressed the very long and difficult processes involved in bringing new drugs to market [25–30]. Similarly, significant parts of the investment community in the City of London have been very skeptical of the claims of a biotechnology revolution, much to the chagrin of the UK government [31].

Second, is there an alternative to the biotechnology revolution model? Historical research suggests that major technological changes, such as those produced by the steam engine, the production line or the electric motor, never take place in a vacuum. They typically required complementary technical and organizational innovations that constrained and structured their adoption [23,32,33]. For example, the diffusion of electricity was hampered by problems with cabling, which was only overcome by innovations in steel production [32]. As a consequence, it can take a long time, typically 40–60 years, for major technologies to produce benefits that even then can be indirect and difficult to detect [23,32]. As Hopkins (D.Phil Thesis, University of Sussex, 2004) demonstrates, early 20th century developments in genetics took many decades to move from the visions of researchers to clinical fruition. Similarly, Benneworth [34] has highlighted the neglected role of slow, incremental, low-tech biotech innovation.

Rather than focusing on biotechnology, an alternative model might conceptualize recent changes in terms of a shift from craft-based to more industrialized experimentation. In a range of procedures including genomics, high-throughput screening, combinatorial chemistry and toxicology, traditional hand-crafted experiments are increasingly being complemented by automated, miniaturized experiments carried out in parallel on populations of samples with complementary analysis of stored and simulated data [35].

Even though this change has made the discovery of small molecule drug targets easier, such improvements cannot be extrapolated to the entire process, because this has only shifted the innovation bottleneck to target validation and clinical evaluation where a much more complex, time-consuming and costly process of research is needed. Such systemic changes have generated a range of novel problems associated with information over-load and statistical quality control. They have led to more interdisciplinary work, an emphasis on speeding up processes and changing organizational structures to maintain output levels. There are parallels here with the problems that Henry Ford encountered when he industrialized production, and it is therefore sobering to realize that the organizational, technical, managerial and social problems that industrializing production generated took many decades to solve.

Whether or not this industrialization model is realistic, it is becoming increasingly clear that advances in basic scientific knowledge do not simply lead to new medical technologies. Clinical research occurs in highly complex and poorly characterized systems (the bodies of human subjects) and medical practice draws on multiple sources of knowledge, only some of which are at present reducible to science. As a consequence, biological knowledge derived in the laboratory is not easily translated into useful clinical practices.

This problem is now starting to be recognized by policy makers. The recent FDA White Paper 'Innovation or

Stagnation' has explicitly stated that: 'Today's revolution in biomedical science has raised new hope for the prevention, treatment and cure of serious illnesses. However, there is growing concern that many of the new basic science discoveries … may not quickly yield more effective, more affordable, and safe medical products for patients.' [36]. In response, the FDA is advocating much greater emphasis on translational and critical path research focused on the clinical assessment of novel products. Initiatives of this kind that address the real problems facing innovators are to be warmly welcomed.

Conclusion

The data we have presented suggests that it is time to rethink the biotech revolution. Policy makers need to follow the FDA and move away from an increasingly discredited linear model of innovation that sees new drug and diagnostic products as little more than the application of basic research. Instead, policy needs to address the uncertain, systemic nature of technical change and the very long time scales between advances in basic knowledge and productivity improvements [23,32,33].

The FDA's emphasis on the importance of getting our facts right is a welcome development because unrealistic expectations have had a major impact on government policy. Undoubtedly, some of the policy suggestions are intrinsically good ideas, such as promoting better knowledge transfer between industry, universities and the healthcare system, but successful policy needs to be based on sound evidence and a sense of proportion. This has not always been the case with biotechnology and there is now a substantial mismatch between the real world and the unrealistic expectations of policy-makers, consultants and social scientists.

Although we have hinted at an alternative model we can say very little at present about the long-term prospects for biotechnology and our data are compatible with a range of eventualities. A pessimistic perspective might highlight that the biotechnology revolution has been closely associated with a reductionist, genetic model of disease [37,38] that is increasingly being challenged by explanations that emphasize the interaction between environmental, lifestyle and biological factors across the life course [27]. Epidemiologists have already noted how the social distribution of a range of common disorders, such as obesity, stomach ulcers and heart disease, has radically changed in the last century, suggesting that the major determinants of these diseases are social rather than purely genetic in origin [39]. These environmental factors, such as poverty and smoking require comprehensive public health programmes rather than unproven high-tech solutions that are unlikely to be delivered in the short term [29]. This uncertainty about the timing and benefits of biotechnology suggests the need for regular checks against the evidence to avoid constructing shared expectations that have little empirical foundation.

Our concern is not the future but the present, and more particularly how current expectations and talk of revolutions help generate the social co-operation needed to deal with the very long-term lead times required to create new medicines. Unrealistic expectations are dangerous as they lead to poor investment decisions, misplaced hope, and distorted priorities, and can distract us from acting on the knowledge we already have about the prevention of illness and disease.

Acknowledgements

This research was funded by the ESRC as part of its Innovative Health Technologies Programme. The authors would like to thank Surya Mahdi, Alison Kraft, Michael Hopkins and three anonymous reviewers. Usual disclaimers apply.

References

1 Bioscience Innovation and Growth Team (BIGT) (2003), Bioscience 2015, DTI London
2 Commission of the European Communities (2002) "Life sciences and biotechnology – a strategy for Europe", Brussels 23/1/2002
3 Organization for Economic Cooperation and Development (OECD) (1997), "Biotechnology and Medical Innovation: Socio-economic Assessment of the Technology, the Potential and the Products" OECD Paris
4 Organization for Economic Cooperation and Development (OECD) (1998), "Economic Aspects of Biotechnologies Related to Human Health Part II: Biotechnology, medical innovation and the Economy: The Key Relationships" OECD Paris
5 Organization for Economic Cooperation and Development (OECD) Committee for Scientific and Technological Policy at Ministerial Level (2004) "Science, Technology and Innovation for the 21st Century", Final Communique meeting 29-30
6 Bell, J.I. (2003) 'The double helix in clinical practice'. *Nature* 421, 414–416
7 Lindpaintner, K. (2002) 'Pharmacogenetics and the future of medical practice'. *Br J Clin Pharmacol.* 54, 221–230
8 Department of Health (2003) *Our Inheritance, Our Future, realising the potential of genetics in the NHS*, The Stationary Office, Norwich
9 Bell, J. (1998) The New Genetics in Clinical Practice. *BMJ* 316, 618–620
10 Collins, F.S. *et al*. (1998) New Goals for the Human Genome Project. *Science* 5389, 682–689
11 Lenaghan, J. (1998) *Brave New NHS?*, IPPR, London
12 Enriquez, J. and Goldberg, R.A. (2000) Transforming Life, Transforming Business: The Life-Science Revolution" March. *Harv. Bus. Rev.* 78, 94–104
13 DTI (1999) *Biotechnology Clusters*, DTI, HMSO, London
14 Tollman, P. *et al*. (2001) *"A Revolution in R&D: How genomics and genetics are transforming the biopharmaceutical industry"*, The Boston Consulting Group, Boston
15 House of Commons Science and Technology Committee (1995) *Human Genetics The Science and its Consequences*, HMSO, London
16 DTI (2001) *Science and Innovation Strategy*, Department of Trade and Industry, London
17 Dohse, D. (2000) Technology policy and the regions – the case of the BioRegio contest. *Res. Policy* 20, 1111–1133
18 Giesecke, S. (2000) The contrasting roles of government in the development of biotechnology industry in the US and Germany. *Res. Policy* 29, 205–223
19 Senker, J. *et al*. (2000) 'European Exploitation of Biotechnology – do government policies help'. *Nat. Biotechnol.* 18, 605–609
20 Horrobin, D.F. (2003) Modern biomedical research: an internally self-consistent universe with little contact with medical reality? *Nat. Rev. Drug Discov.* 2, 151–154
21 Horrobin, D.F. (2001) Realism in drug discovery – could Cassandra be right? *Nat. Biotechnol.* 19, 1099–1100
22 Mahdi, S. (2004), The Pharmaceutical Industry, Unpublished Bibliometric Dataset SPRU, University of Sussex, UK
23 Rosenberg, N. (1979) Technological Interdependence in the American Economy. *Technol. Cult.* 20, 25–51
24 Arundel, A. and Mintzes, B. (2004), The Impact of Biotechnology On Health, Merit-Innogen Working Paper, Innogen, University of Edinburgh-Open University
25 Nature Editorial. (2003) Facing Our Demons. *Nat. Rev. Drug Discov.* 2, 87

26 Williams, M. (2003) Target Validation. *Curr. Opin. Pharmacol.* 3, 571–577
27 Drews, J. (2003) Strategic Trends in the Drug Industry. *Drug Discov. Today* 8, 411–420
28 Kubinyi, H. (2003) Drug Research: Myths, Hype and Reality. *Nat. Rev. Drug Discov.* 2, 665–668
29 Triggle, D.J. (2003) Medicines in the 21st Century Or Pills, Politics, Potions, and Profits: Where Is Public Policy? *Drug Dev. Res.* 59, 269–291
30 Lindpainter, K. (2002) The impact of pharmacogenetics and pharmacogenomics on drug discovery. *Nat Rev Drug Discov.* 1, 463–469
31 Pratley, N. (2003) 'The Drugs Don't Work'. *The Guardian*. 23rd November
32 Freeman, C. and Louca, F. (2002) *As Time Goes By: From the Industrial Revolution to the Information Revolution*, Oxford University Press
33 David, P. (1990) The Dynamo and the Computer: An Historical Perspective on the Modern Productivity Paradox. *Am. Econ. Rev.* 80, 355–361
34 Benneworth, P. (2003) Breaking the mould: new technology sectors in an old industrial region. *Int. J. Biotechnol.* 5, 249–268
35 Nightingale, P. (2000) 'Economies of Scale in Experimentation: Knowledge and Technology in Pharmaceutical R&D'. *Ind. Corp. Change* 9, 315–359
36 FDA (2004) *Innovation or Stagnation, Challenge and Opportunity on the Critical Path to New Medicinal Products*, U.S. Department of Health and Human Services, Food and Drug Administration
37 Charkravarti, A. and Little, P. (2003) Nature, Nurture and Human Disease. *Nature* 421, 412–414
38 Lewontin, R. (1993) *Biology as Ideology: The Doctrine of DNA*, Perennial, New York
39 Wilkinson, R. (1997) *Unhealthy Societies: The Afflictions of Inequality*, Routledge