Introduction

Luigi Orsenigo*

DIMI, University of Brescia,
Via Branze, 38,
Brescia 25123, Italy

Cespri, Bocconi University,
The Grafton Building,
Via Roentgen 1,
Milan 20136, Italy

ESRC INNOGEN Centre,
Open University,
Walton Hall,
Milton Keynes MK7 6A, UK
E-mail: luigi.orsenigo@unibocconi.it
*Corresponding author

Joyce Tait

ESRC INNOGEN Centre,
University of Edinburgh,
Old Surgeon's Hall,
Edinburgh EH1 1LZ, UK
E-mail: joyce.tait@ed.ac.uk

Biographical notes: Luigi Orsenigo is a Professor of Industrial Organization at the University of Brescia, Italy and in 2007–2008 at the Open University, UK. He is also Member of the Board of Directors of CESPRI, Bocconi University, Milan in Italy. After receiving his PhD from the Science Policy Research Unit, University of Sussex in 1989, he has been affiliated with Bocconi University and the University of Brescia. His work concerns mainly, the economics of innovation, industrial dynamics and the bio-pharmaceutical industry. His publications include The Emergence of Biotechnology, Pinter Publishers, London, 1989; The Economics of Biotechnology (editor, with M. McKelvey), Edward Elgar, Cheltenham, 2006 and several papers on major international journals. He is Editor of the *Journal of Evolutionary Economics*. He has been advising several Italian and international institutions on matters of innovation and industrial policy.

Joyce Tait is a Scientific Adviser of the ESRC Innogen Centre and a Professor at the University of Edinburgh. She has an interdisciplinary background in natural and social sciences covering: technology development strategies in the chemical and life science industries (including agro-biotechnology and pharmaceuticals), translational medicine; governance, risk assessment and regulation; policy analysis; stakeholder attitudes and influences; science and risk communication. She is a Fellow of the Royal Society of Edinburgh and also of the Society for Risk Analysis. Her recent and current external appointments include: Scottish Science Advisory Committee, Scientific and

Technical Council of the International Risk Governance Council, Geneva, Member of the Board of Directors of the Scottish Stem Cell Network Ltd., Member of the Governing Council of the Roslin Institute and President, Society for Risk Analysis – Europe.

1 Introduction

In February 2005, Innogen, the ESRC Centre for Social and Economic Research on Innovation in Genomics based in the University of Edinburgh and at the Open University, organised in Edinburgh a lively, thought-provoking and highly successful international conference on the Evolution of the Life Science Industries. The broad aim of the conference was to reflect upon the problems that these industries were facing and the role that the new technologies (such as genomics, stem cells, bioinformatics) could play in further transforming the landscape, in terms of opportunities for innovation but also challenges for conventional business models, policies and regulation.

Indeed, the conference could not have been held at a more timely moment. The pharmaceutical industry was showing symptoms of profound stress in terms of innovativeness, profitability and public image. Soaring costs of R&D were not being matched by an adequate flow of new innovative products launched on the market, denoting a significant fall in R&D productivity. The reputation of the industry was being severely tarnished by disputes over intellectual property rights and the prices of drugs, episodes of withdrawals from the market of highly successful drugs, not to mention the uproar caused by the Pretoria trial: 411 companies had sued the South African government in the person of Nelson Mandela for passing a law opening up the import market to cheap copies of brand name ARV/HIV medicines but they were later forced to drop the case under the pressure of the international public opinion. In parallel, cost-containing policies were trying to limit public expenditure on healthcare and on drugs in particular. In the USA, the issue of the reform of the healthcare system was becoming a priority and a bitterly debated issue in the political arena. At the global level, feelings were spreading that the entire system of providing medicines and healthcare to those in need was deeply flawed, since it was too heavily biased towards 'rich' markets and diseases.

As a consequence, the traditional business model which had successfully characterised the pharmaceutical industry for many decades was being put under question. Questions were raised whether the large, vertically integrated companies could still sustain innovation when scientific and technological progress was increasingly originating – and at a very fast rate – from universities, public research organisations and small specialised firms. Indeed, it was noted that an increasing share of the new drugs, that had been developed through research and licensing agreements with these organisations and networks of alliances, had become in the recent past a distinctive feature of the industry. Large pharmaceutical companies were increasingly outsourcing clinical trials. Equally, it was being asked whether the blockbuster model was still viable in a new environment where the costs and risks of R&D had become so high and where the diffusion of evidence-based medicine and the promises of genomics might create the conditions for personalised drugs (Tait, 2007).

Thus, it was timely to investigate how these developments in the pharmaceutical industry could interact with the rapid evolution of life sciences. Indeed, in more recent years, new waves of scientific and technological advances have provided the life-science industry with new opportunities, challenges and threats. In the late 1970s and 1980s, genetic engineering had opened the way to the possibility of developing new drugs, which were previously difficult and costly to produce through conventional methods. Thus, companies (both incumbents and new entrants) successfully brought to the market 'large molecules' like growth hormone, insulin and clotting factor VIII. In 1990s, the advent of the so-called platform technologies (combinatorial chemistry, high-throughput screening and computational chemistry) led to what has been termed 'industrialised R&D' (Pisano, 2006), offering the potential to understand and identify much more precisely the causes of diseases, to create new compounds, to screen them much more efficiently and to design rationally drugs with specific effects. Further progress in genomics and bioinformatics as well as research on stem cells are now adding new frontiers to innovation.

In particular, the time was ripe to examine how such progress could further transform the industry, possibly for the better.

However, the prospects are not as clear and simple as would appear at first sight. Not only Big Pharma, but also the biotechnology segment of the industry was under stress. And it is perhaps useful to reflect upon the history of biotechnology in order to draw some insights on the deep conceptual issues which underlie an analysis of the current situation.

The birth date of the so-called biotechnology industry is customarily identified as 1976, when Genentech – the first specialised biotechnology company – was founded by a scientist and a venture capitalist. Biotechnology as a technology and biotechnology as an industry immediately sparked tremendous interest and expectations, attracting huge investment and human resources. The expectations were that the new scientific breakthroughs would lead to revolutionary technological progress in a wide variety of sectors and fields, ranging primarily from pharmaceuticals but encompassing also agriculture, food, energy, etc. Moreover, it was thought that the new opportunities for technological innovation would generate enormous profits and welfare. The economic exploitation of these benefits would have largely been reaped by a new breed of companies – a new industry – specialised in transforming the new scientific knowledge into new products, possibly displacing the old, large incumbents that were dominating the relevant industries. Governments all over the world have identified biotechnology as a key target for support and have devised a stunning variety of schemes and actions to support what is perceived to be one of the key technologies of the 21st century, able radically to transform healthcare and many other important sectors of the economy.

More than 30 years have passed since that momentous event. The Brothers Wright made the first controlled, powered and sustained heavier-than-air human flight on 17 December 1903. Since then, it took only 65 years to land the first man on the moon. Seen from this perspective the biotechnology industry is certainly not a new industry any longer and one could also argue not a particularly successful one, if success is measured in terms of new products and profitability.

Indeed, highly influential scholars like Gary Pisano have claimed that the biotechnology industry has substantially failed to deliver its promises (Pisano, 2006).

Firstly, the biotechnology revolution has made its mark mainly in pharmaceuticals and, to a lesser and much more controversial extent, in agro-food. The impact in other

industries, while certainly relevant, has been much less profound. In particular, the widely held view that biotechnology could constitute a new knowledge base offering opportunities for diversification has so far been defied: on the contrary, we have been observing strong tendencies toward extreme levels of specialisation in very narrow scientific and technological niches.

Secondly, the new companies have not displaced the old incumbents. Most of the new firms have essentially become specialised suppliers of specific knowledge to large corporations, giving rise to a dense network of alliances and collaborative relationships and markets for knowledge. But only a tiny fraction of biotech companies (Genentech, Amgen, Genzyme, Biogen Idec) have ever been profitable or even able to produce positive cash flows. The few successful companies are typically early entrants in the industry and their business model is quite different from what was – and largely still is – conceived as the hallmark of the new 'Dedicated Biotechnology Firm' (DBF): they have indeed transformed themselves into quasi-conventional pharmaceutical companies, vertically integrated into manufacturing and marketing. On the other hand, large pharmaceutical companies have been able gradually to absorb the new knowledge, mainly using it as a tool to enhance the productivity of the discovery of conventional 'small molecule' synthetic chemical drugs (Henderson et al., 1999).

Thirdly, as mentioned previously, the productivity of pharmaceutical R&D has not improved. If anything, quite the contrary. While a growing fraction of the new compounds tested and launched in the market now originates from the new science and from research conducted by biotechnology companies licensed to larger corporations, still over the period 1978–2003, research 'productivity' measured by the number of patents per dollar of R&D expenditure, actually fell: R&D expenditure increased tenfold, while patenting output increased only sevenfold. This is further corroborated by the number of new chemical entities (a much more demanding measure of innovativeness than patents) approved by the FDA in the USA over the period 1983–2003: some increase is recorded until the mid 1990s, followed by a sharp decline subsequently. So, in 2002, US R&D expenditures in pharmaceuticals were 30 times greater than in the early 1980s, while roughly the same number of drugs were approved annually. Similarly, Pisano (2006) shows that the number of compounds developed by commercial organisations that have progressed at least to human clinical testing has not increased significantly since the advent of the biotechnology revolution and the subsequent wave of technological advances which are usually defined as 'platform technologies'.

Finally, while the biotech industry has spread in many countries – and as we shall argue at more length afterwards, regions – still it has proven remarkably difficult to even catch-up with the leadership of the USA and, in particular, some US regions: the Boston area, the San Francisco Bay area and San Diego. If anything, all kinds of available data – bibliometric, patents, number of firms, companies structural and performance data, etc. – indicate that biotechnology is perhaps even more concentrated in a few regions in the USA than it was in the late 1970s and early 1980s.

To be sure, the whole history of pharmaceuticals and biotechnology has been marked by periods of hype and pessimism. Its development over time has been driven and characterised by waves of new scientific and technological advances, which have continuously redefined the opportunities for innovation, business models and market structure. Public policies and public perception have always had a crucial role in the evolution of the science, of the related technologies and of their industrial applications. Partly as a result, stock exchange valuations and venture capital funding have shown

sharp fluctuations. But many of the issues that are so hotly debated today were discussed decades ago at the time of the Kefauver Commission in the USA.

Thus, it is worthwhile to take stock and to reflect upon a few crucial issues which are suggested by these developments.

Firstly, what are the causes of the slowdown in pharmaceutical R&D productivity? And how is the evolution of market structure and firm's organisation linked to this phenomenon?

Secondly, how can the new generation of 'promises' offered by scientific progress in the life sciences be realised through new products and what are the obstacles, especially as they relate to public policies and public perception?

Thirdly, how has the geography of biotechnology been evolving and what are its prospects?

Finally, what kind of public policies can be effective in spurring the development and maturation of the biotechnology industry at the local level?

The papers in this Special Issue of the IJBT address these questions and offer a significant contribution to the debate as well as an extremely useful review of the state-of-the-art. Even more so, as these questions raise important issues for the economics of innovation in general, these papers contribute to a more general investigation into the contemporary patterns of technological and industrial progress.

2 Falling innovation rates and changes in firms' and industry organisation

The decline in pharmaceutical R&D productivity is well documented but there is considerable disagreement about its causes and its seriousness. As discussed in the papers by Christopher-Paul Milne and by James Mittra, some interpretations are relatively optimistic, emphasising that the production of new drugs is characterised by strong cyclical components. The current downswing might therefore be considered as a temporary phenomenon, bound to be reversed in the near future, as some indicators would already suggest. Yet, one is still left to wonder about the rising costs of R&D and the disappointing impact of the new scientific knowledge and related technologies upon the rate of introduction of new drugs.

Regulation is often blamed for rising costs and dwindling productivity. There is little doubt that expanded numbers of trials, patents and procedures to meet regulatory requirements have significantly contributed to the increased costs and time of product development. Yet, substantial progress has also been achieved in shortening development times on the regulatory side, particularly for specific classes of drugs. While certainly much remains to be done in increasing the efficiency of the regulatory process, a key issue remains that preclinical times have increased and success rates are too low.

Thus, another interpretation suggests that the decline in productivity could be the outcome of an intrinsic difficulty in discovering new drugs for increasingly complex pathologies: the low hanging fruits have already been picked and now the challenge becomes harder. In this respect, the stagnation in innovative output would be the outcome of an incumbent 'maturity' of the industry (Nightingale and Martin, 2004), characterised by a fall in innovative opportunities – a little like the mature phase in the life cycle of such industries as steel or automobiles (Klepper and Simons, 1997). Along similar lines, the view is also proposed that pharmaceutical companies have moved away

from truly innovative research, concentrating on the development of me-too-drugs and minor improvements upon existing products (Angell, 2004). As Milne reports in his paper, various analysts suggest that now big pharma does little more than serve as a manufacturing and especially marketing giant feeding off the innovation seedbeds of small biotechs and academic research.

Whether this contention contains elements of truth or just fails to recognise the crucial role played by large organisations in the innovation process, characterising pharmaceuticals as a mature industry still looks awkward in the face of the tremendous pace of scientific and technological progress. However, even the new fundamental knowledge might not be sufficient to overcome these obstacles in the short and medium term. Indeed, Mittra in his paper and Nightingale and Mahdi (2006) suggest that the biotechnology 'revolution' has not, in fact, increased the observed productivity of R&D because of the inability of drug firms to keep pace with the increased intrinsic complexity of the biochemical problems that innovative search is addressing. One could also argue along similar lines that the biology revolution in drug discovery and drug making has not only provided researchers with a better understanding of the possible fundamental causes of diseases and therefore of the possible treatments, but it has also implied an explosion of the space of search. Moreover, the 'new science' is still largely in its infancy. In particular, as Mittra emphasises, enormous bottlenecks remain between the explosive growth of available experimental information made possible by the scientific revolution and the ability to use that knowledge for developing new drugs, especially at the target validation stage. Thus researchers are now confronting and tapping a multitude of unexplored and highly uncertain areas: opportunities for innovating are growing, but their actual realisation becomes more costly and difficult as there is much more to understand and explore than previously imagined (Orsenigo et al., 2001).

As Milne argues in his paper, this interpretation is to a considerable extent reflected in the FDA Report 'Innovation or Stagnation', which emphasises in particular that development sciences have not kept up with advances in discovery sciences. The bottleneck is identified in this view in the development phase, rather than in the discovery stage and suggestions are advanced to improve on the current situation.

This interpretation is also intuitively in tune with the more general observation that new technological paradigms take time to establish themselves, and their diffusion into the economy requires concomitant changes in the whole organisational and institutional structure of the economy (David, 1990; Freeman, 1995). It may well be that new products are still in their infancy with respect to their full potential uses throughout the economy as happened with electricity, cars and the PC, when it took almost 30 years for the new product to be adopted by mainstream businesses and consumers (Wong, 2005). Thus, the stress and the changes which are observed in the organisational and regulatory structure of the industry could be understood as processes of painstaking coevolution of technology, organisations and institutions to the technological revolution.

Against this background, it is clearly very hard to predict how the industry will look in the next 10 to 20 years. The question concerns the viability of the traditional business model as incarnated in big pharma but also the fate of the biotechnology sector. Can big pharma companies continue to be crucial agents in the innovative process, along – and interacting – with academia and biotech companies? Can (or should) this specialised segment of the industry survive as supplier of basic knowledge and research tools for

larger organisations without further downstream vertical integration? Or could the same function be performed by universities and other public research centres, going back to a more reasonable intellectual property regime which promotes open science?

Theoretical work and empirical evidence on this issue provide somewhat conflicting views and no definite conclusions. At one extreme, the benefits emphasised are related to a deepening division of innovative labour between companies specialised in the 'exploration' phase and larger organisations controlling the complementary assets necessary for the development and marketing of the potential new products (the 'exploitation' stage) (Arora et al., 2001). At the other extreme, it is stressed that the very process of industrialisation of pharmaceutical R&D, with high fixed costs of drug discovery and experimentation – raises the economic benefits and the need to integrate highly specialised, multidisciplinary knowledge. Similarly, the enormous risks involved in this kind of research can be more effectively managed by more long-term oriented investment, less dependent on the creation of high expectations based on highly incomplete information (Nightingale and Mahdi, 2006; Pisano, 2006).

Indeed, increasing evidence suggests that industry structure has been evolving towards a hierarchical structure where large corporations perform the crucial function of integrators of the different fragments of knowledge and capabilities that are required to produce a new drug, surrounded by cohorts of new firms that act as suppliers of highly specialised techniques (Orsenigo et al., 2001). In other words, increasing division of labour has created the need for stronger integration of knowledge. As had happened in other industries, however, deepening division of labour raises the risk that large firms progressively lose their innovative capacities, and even their 'absorptive capacities', that is, the ability to understand, evaluate, and absorb new, externally created knowledge. Should this happen, the large established pharmaceutical companies might become essentially marketing-based organisations, the function of which is 'simply' to conduct clinical trials, get approval for the products and sell them. But the question remains whether innovative products can be discovered and developed by small, highly specialised and often transient organisations. As Milne notes, genomics and personalised medicine might provide the industry with the right answer to current problems. James Mittra discusses in his paper two important examples of the attempts by large pharmaceutical firms to cope with the challenges posed by dwindling productivity and high attrition rates. Despite their profound differences, these reactions involve more decentralised R&D models and increasing emphasis on translational medicine. Whether these organisational and strategic changes will be sufficient to revitalise the industry remains to be seen. But both historical experience and theoretical understanding suggest that fulfilling this promise will entail further profound transformations at the technological, organisational, institutional and political level.

3 Realising the prospects of genomics: visions and industry evolution

As Alison Kraft and Harry Rothman argue in their paper, the Human Genome Project was the 'most extravagantly hyped scientific research programme since the moon-shot of the 1960s'. Building on our previous comparison between the development of biopharmaceuticals and the aerospace technology, it is to be hoped that progress in genomics is as fast as in aerospace and that soon we shall be able to land on the moons

that are awaiting us. The analogy stops here, though. If the Moon Project was to a large extent an engineering problem, genomics is still a poorly understood scientific endeavour, where our knowledge of the basic principles is strikingly limited. Moreover, the moons to be conquered are not deserts, but are populated by suffering people. And, as Richard Nelson pointed out many years ago, landing on the Moon was much easier than addressing the problems afflicting the ghettos.

Kraft and Rothman illustrate how the development of genomics as an 'industry' was driven by complex interactions between expectations, commercial push and clinical pull. They show also how the volatility of those expectations have had profound impacts on investment, business models and research trajectories. Their paper in this Special Issue emphasises, in particular, how changing visions about the potential of the technology bear important implications for the expectations and therefore for the realisation of such potential. While grounded in history and sociology, this line of analysis is not inconsistent with the 'technological paradigms, trajectories and regimes' approach, whereby technological paradigms define the problems that are to be solved, the strategies and techniques necessary for the solution, the trajectories of advancement and also the ways through which innovation is organised and proceeds (Breschi et al., 2000; Dosi, 1982; Nelson and Winter, 1982). Indeed, scientific progress (to a large extent consisting in demonstrating that some assumptions and conceptualisations were wrong, rather than immediately producing discoveries) leads to different conceptualisations of what the paradigm can deliver and how. Market structure, business models and the organisation of R&D change accordingly. In a nutshell, the nature of knowledge heavily influences the pace, direction and structure of innovation. On the other hand, highly consistent with these views is the notion that 'history matters' in the evolution of science, technology and industrial innovation. Thus, the development of genomics has been critically dependent on the prior history of the earlier stages of biotechnology, inheriting and further exploiting the organisational innovations and the institutional set-up formed in the 1980s, based on a tight intellectual property regime, venture capital, alliances and networks between new specialised companies and large incumbent drug producers.

Thus, in many respects, the development of genomics resembles quite closely the earlier history of biotechnology. However, important differences exist also, illustrating at an even finer level of detail how the nature of the knowledge base and the associated learning process map onto the organisation of R&D. In particular, the first generation biotechnology companies – based on r-DNA and antibody hybridisation techniques – were mainly in the business of producing specific proteins whose properties were well understood. Most of these companies, if successful, were aiming at becoming integrated drug producers. As scientific knowledge progressed along this trajectory, new companies were formed on the basis of highly specialised techniques which could be useful for the development of equally highly specific projects. These companies lived by forging agreements with larger pharmaceutical companies as specialised suppliers interested in those particular research directions. The outcome was a strongly hierarchical network of alliances where larger and older companies attracted relationships with different younger firms (Orsenigo et al., 2001). With the advent of genomics and more generally platform technologies and industrialised R&D, this pattern changed significantly. This new generation of entrants was developing techniques which were potentially relevant for a wide variety of different projects and companies. As Kraft and Rothman emphasise, they were operating upstream along the supply chain. As a consequence, the structure of the network of relationships changed accordingly, with this new breed of firms interacting with a much larger variety of different agents

and substantially weakening the hierarchical structure of the network. The latest developments in genomics, with the transition from structural to functional genomics, is again spurring specialisation and downstream orientation, with larger organisations acting as knowledge integrators. The network of alliances is likely to change its structure again.

4 The role of regulation and public perception: the case of stem cells

A further fundamental set of variables influencing technological change and its industrial applications concerns regulation and public perception.

There is no need to emphasise here how the whole history of pharmaceuticals has been marked by acrimonious debates on how much and through which instruments the industry had to be regulated. As mentioned previously, these issues were thoroughly discussed in the 1960s at the times of the Kefauver Commission in the USA but in many other countries as well. Various studies hold the view that the structure of regulatory systems, even as it concerns seemingly minute details, can go a long way to account for the different performances of the pharmaceutical industry in countries such as UK, France, Japan and Italy (Thomas, 1994).

The growth of the biotechnology industry has been even more prominently influenced by regulation and public perception. It could be argued that biotechnology as an industrial activity is largely the outcome of a series of key institutional and regulatory decisions, concerning, for example, the patentability of living organisms and the spread of a very permissive attitude towards the commercialisation of open science. Similarly, the differential evolution of pharmaceutical and agro-food biotechnology has been significantly determined by diverging public attitudes towards applications in those domains (Tait et al., 2006).

Stem cell research is a further and perhaps extreme case of how public perception, legislation and regulation can promote or hinder technological development – for the good or for the bad. The paper by Bower, Murad, Sulej and Tait examines these hurdles, focusing in particular on public perception as proxied by media coverage and rhetoric.

The paper makes several important observations. Firstly, the authors show how the limited private investment in this line of research – as a consequence of the technical and regulatory uncertainties surrounding the potential applications – is partly compensated by public and above all charitable funding: a situation which is becoming a crucial development in many other fields of biomedical research (such as vaccines), and raises important and thorny questions about how R&D should and could be organised in the many fields where profit-driver investment is lacking.

Secondly, the paper by Bower et al. emphasises how the reduction of technical and regulatory uncertainties may not be enough to attract investment into a controversial technology. The cases of renewable energy technologies and nuclear power generation are mentioned as examples of how public perception and the formation of pressure groups of various sorts can profoundly influence the economic and political viability of new technologies. Genetically modified crops are clearly a further example of the thorny issues surrounding the 'democratic control' of technological progress.

Thirdly, however, in the case of stem cells, although public acceptability of the technology is by no means universal, it does not at present appear that therapeutic

applications are likely to meet with strong opposition. Despite US President Bush's decision to block Federal funding to research using human embryonic stem cells, public opinion remains divided and individual states in the US have been setting up their own support schemes. Moreover, public opinion does not appear to be concerned too much by ethical issues, at least in the UK but also in the USA, whereas in other countries, Italy being a classical example, perceptions might be more hostile.

In any case, the example of stem cell research indicates clearly how technology, regulation and public perception coevolve over time. As proposed by Tait et al. (2006), regulation of new emerging technologies can be classified as

1 enabling or constraining

2 discriminating versus indiscriminate among products

3 product versus process based, in relation to the perceptions of managers and companies.

Moreover, it is increasingly perceived that regulation should move from a traditional government approach which is typically characterised by constraining, indiscriminate and product-based initiatives to a governance approach, which would include enabling, discriminating and process-based policies and instruments. In this respect, one observes important differences between countries as it concerns the emerging regulatory system for stem cells. For example, in the USA stem cells are essentially viewed and treated as products, implying that they will be treated as drugs for regulatory purposes. In Europe, stem cells were initially likely to be treated as devices and therefore regulated as analogous to surgical procedures, although recently it has been confirmed that the EMEA will be the body charged with regulation of stem cell-based therapies (Bonnicksen, 2002; Faulkner et al., 2003; Tait et al., 2006). One might speculate that these different perspectives could create a more favourable regulatory climate in Europe and therefore a potential competitive advantage, although at the moment it would be foolish to commit to strong predictions. Yet, reflecting upon how new technologies can be regulated and governed in a progressive and democratic way appears to be one of the most important and difficult tasks ahead.

5 Clusters and catching up

As we noted earlier, the development of the biotechnology industry has been characterised by high and persistent concentration at the geographical level. Since its outset, the industry has been strongly clustered in few regions in the USA and it has proven remarkably difficult for other regions to catch up. Despite the growth of new clusters around the world, innovative and industrial activities in this sector remain strongly clustered in the original areas where they were first developed.

These observations raise several interesting but difficult questions. What are the processes leading to persistent clusterisation? Are they similar to or different from the conventional explanations of the processes of geographical concentration of innovation and production in other technologies and industries? Why it has proven so hard to catch up?

The conventional literature on clusters has concentrated on explanations which are essentially various reformulations of the fundamental sources of agglomeration

externalities originally suggested by Marshall (see Henderson (1986) and Krugman (1991) among others). They include economies of intra-industry specialisation (a localised industry can support a greater number of specialised local suppliers of industry-specific intermediate inputs and services, thus obtaining a greater variety at a lower cost); labour market economies (a localised industry attracts and creates a pool of workers with similar skills, which benefits both the workers and their employers) and ease of communication among firms (information about new technologies, goods and processes seem to flow more easily among agents located within the same area, thanks to social bonds that foster reciprocal trust and frequent face-to-face contacts). Therefore adoption, diffusion and innovation seem faster and more intense in geographical clusters than in scattered locations. In other words, 'knowledge spillovers' exist, which are geographically bounded.

Other explanations stress the geographical embeddedness of flows of knowledge. Hence, in some views, clusters are often associated with cooperation in innovative activities and interactive learning (Cooke, 2002; Maskell, 2001). According to this view, firms within innovative clusters learn through a variety of types of interactions, ranging from user-producer relationships, formal and informal collaborations, inter-firm mobility of skilled workers and the spin-off of new firms from existing firms, universities and public research centres. Local firms are embedded in a thick network of knowledge sharing, supported by close social interactions and by (formal and informal) institutions that promote the development of trust among participants in the network.

However, as argued in the paper by Phil Cooke, biotechnology clusters seem to have specific characteristics.

Firstly, they are science driven. Thus, excellence in scientific research spanning a differentiated spectrum of areas as well as an integration along the horizontal and vertical dimensions of the innovative process are crucial ingredients for the development of biotechnology. Without these capabilities, the role of other factors appears to be ancillary.

Secondly, biotech clusters involve the establishment of dense networks of interactions among differentiated agents (e.g. academic researchers, large corporations, specialised biotech firms, venture capitalists), each of them controlling only fragments of the knowledge, resources and capabilities necessary for exploring and commercially exploiting the opportunities created by scientific advances. Thus, clusters are characterised by strong elements of collaboration as well as by competition and, more generally, they are based on processes of construction and integration of specific capabilities.

Thirdly, however, biotechnology can hardly be interpreted as a case where knowledge within a cluster simply 'spills over'. Rather, access to such knowledge seems to require deep involvement in the research process and bench-level scientific collaboration as well as the conscious investment of resources not simply to search for new knowledge but to build the competencies to absorb the knowledge developed by others. In many cases, knowledge flows occur via (localised) mobility of researchers and of the workforce. These 'flows' are mediated by market transactions and other institutionalised or quasi-institutionalised mechanisms involving not simply mutual trust and face-to-face contacts, but also highly complex economic and social structures. Indeed, knowledge tends to remain sticky within biotech clusters for reasons related to attempts to privately appropriate knowledge and restrict its circulation. Thus, in these clusters knowledge is not simply 'in the air'. Similarly, in contrast to other accounts of

clusters, 'soft' factors like trust seem to play an important but not predominant role, given that knowledge flows in the biotechnology industry appear to be channelled significantly through market transactions and inter-organisational rules.

Fourthly, and mainly as a consequence of the crucial role played by science, biotechnology clusters are not simply local, but they are strongly open to interaction with other firms and institutions located throughout the world. In other words, biotech clusters are not strongly geographically embedded – they are eminently global in nature.

Finally, however, for the same reasons, biotech clusters have a distinct hierarchical nature. Scientific excellence is strongly concentrated in a few regions and this generates and attracts new opportunities, funding (both from venture capital and large corporations) and new firms. Thus, dominant bioregions strengthen their leadership. As scientific capabilities diffuse and grow in other locations new, smaller and more specialised clusters appear but they cannot displace the old ones. Rather, they link – scientifically and commercially – with the existing 'megacentres'.

The same hierarchical structure observed at the geographical level is also visible at the industrial level: the network of alliances among firms and other research centres exhibits the same properties (Orsenigo et al., 2001). Indeed, this is likely to be the outcome of the very nature of the processes of scientific advance and of the processes of construction and integration of innovative and industrial capabilities. They both involve first mover advantages and self-reinforcing tendencies which give rise to hierarchical structures with some firms and clusters performing as 'integrators' of spatially dispersed and specific knowledge, research tools and capabilities. In this respect, geographical agglomeration results not only as an outcome of traditional externalities but also (and perhaps mainly) as a result of increasing returns, whereby clustering results from processes of spin-off (as distinct from spillovers) from knowledge-rich organisations (Klepper, 2002; Orsenigo, 2006).

6 Can clusters be built?

The question remains as to whether clusters – and more generally a biotechnology industry – can be built through policies and public support. Attempts at stimulating the development of biotechnology as an industry have been undertaken almost everywhere in the world, often with an explicit emphasis on clusters. Results are mixed, of course, but probably closer to failure than to success. Yet, as Cooke shows, success stories exist and in some of these cases public intervention has been crucial in determining a positive outcome: Singapore is an obvious example, but – in rather different ways – also in Israel, Germany, Sweden, France and Washington, DC the role of the public sector and public investment has been crucial for the stimulation of research activities and their commercialisation.

Thus, the original question could be reframed as "what kind of policies and what kind of preconditions are necessary to support the development of biotechnology, especially at the local level?"

The paper by Alessandro Rosiello goes to the heart of this question, focusing on the case of the Scottish Enterprise Framework for Action in Life Sciences. Rosiello contrasts two types of approaches. The first one considers policy action – in a rather orthodox way – as a response to the market failures associated with innovative activities, that is, mainly the public good aspect inherent in R&D. Here, the scope of public

action is identified in the reduction of the risk associated with R&D investment and in granting protection over intellectual property. A second approach – the systemic approach – stresses that the performances of individual agents do not uniquely depend on the way markets operate. Rather, innovation is the outcome of the ways in which agents cooperate and learn. Thus, innovation policy should be increasingly aimed at improving connectivity between actors holding complementary fragments of knowledge, resources and capabilities.

In a complementary way, one might identify two further typologies of intervention. On the one hand, it is possible to distinguish between actions aimed at making available the crucial ingredients that are necessary for a successful cluster; and interventions focusing on the processes by which such ingredients interact with each other and might end up generating self-sustaining growth and innovation (Orsenigo, 2006). On the other hand, policies can be primarily oriented towards creating incentives to innovation as contrasted with measures attempting to create capabilities and opportunities for innovation.

Although the overlap is far from perfect, 'market failure policies' tend more frequently to act on the 'ingredients' and the 'incentives', while 'systemic policies' are likely to target the 'processes' and 'capabilities'.

According to Rosiello, Scottish Enterprise has implemented a policy mix which attempts to work on all these different directions and objectives, albeit with different emphases and outcomes over time. Attempts to improve the existing infrastructure and provide financial support to new ventures have led to the formation of a significant number of new private ventures and the number of people and organisations currently active has doubled in the period 1999–2003. A significant pool of skilled labour and intermediaries is also in place, while flows of useful information seem to affect the strategy of a considerable proportion of Scottish DBFs. However, there is little evidence so far that sizeable external ('Marshallian') economies have been created benefiting the local industry. Similarly, only partial success has been obtained by policies directed at promoting networking, incremental dynamics and increasing returns.

These findings are consonant with, and significantly add to, earlier results obtained for other countries and regions which emphasise the opportunities and the difficulties in sparking processes of technological and innovative growth in high tech industries. In particular, as Bresnahan et al. (2001) put it, our current knowledge is much better able to provide hypotheses about how a cluster keeps going than in explaining the nature of the spark that generate the cluster itself. They suggest that emerging clusters tend to share some common features: existence of unexploited, technological and market opportunities, highly educated skilled labour, firm- and market-building capabilities by pioneering firms, connection to markets and luck. Another recurrent factor is the availability and concentration of state-of-the-art knowledge in key agents. Interestingly, variables such as the presence of supporting institutions (e.g. venture capital) and the diffusion of particular social attitudes (e.g. entrepreneurship) appear to play a much lesser role in nascent clusters: if anything they tend to develop later on as a product of the agents' activities.

Conversely, the developed, successful clusters appear to profit from the concomitant presence of all the ingredients, although their role and specific nature varies significantly. Yet, in many cases, these ingredients were not simply in place simultaneously at the beginning, that is, at the time of the genesis of the cluster. Certainly, those locations where most of these conditions are or were available enjoy(ed) significant advantages.

But this is neither a necessary nor a sufficient condition. Rather, in almost all cases, the process of construction of such ingredients would seem to be a crucial part of the story: in a sense the process is a fundamental ingredient itself.

Putting it another way, clusters are born and develop on the basis of specific combinations of capabilities, incentives and opportunities. The three elements are inseparable and linked to each other in intricate ways. Competencies obviously contribute to creating and defining opportunities as well as the ability to take advantage of existing opportunities. The latter feed back on the processes of accumulation and development of new competencies. Competencies without incentives remain unused. But incentives without sufficient capabilities are sterile and might even be destructive. More interestingly, particular sets of capabilities identify sets of appropriate incentives, which in turn and once again influence the speed and directions of the processes of accumulation of competencies. Understanding how the different dimensions of policies match with each other would require sophisticated taxonomical exercises and hard theorising. But intuitively it should come as no surprise that 'systemic-process-capabilities' policies operate on a different time scale and on a higher degree of complexity than 'market failures-ingredients-incentives' interventions. Unravelling these interactions appears to be a fundamental chapter in the agenda of future research.

References

Angell, M. (2004) *The Truth About the Drug Companies: How they Deceive us and what to do about it*, New York: Random House.

Arora, A., Fosfuri, A. and Gambardella, A. (2001) *Markets for Technology*, Cambridge, MA: MIT Press.

Bonnicksen, A.L. (2002) *Crafting a Cloning Policy: From Dolly to Stem Cells*, Washington, DC: Georgetown University Press.

Breschi, S., Malerba, F. and Orsenigo, L. (2000) 'Technological regimes and Schumpeterian patterns of innovation', *The Economic Journal*, April.

Bresnahan, T., Gambardella, A. and Saxenian, A. (2001) 'Old economy inputs for "New Economy" outcomes: cluster formation in the new Silicon Valleys', *Industrial and Corporate Change*, Vol. 10, No. 4, pp.836–860.

Cooke, P. (2002) *Knowledge Economies: Clusters, Learning and Cooperative Advantages*, London: Routledge.

David, P.A. (1990) 'The dynamo and the computer: an historical perspective on the modern productivity paradox', *American Economic Review*, Vol. 80, No. 2, pp.355–361.

Dosi, G. (1982) 'Technological paradigms and technological trajectories', *Research Policy*, Vol. 11, pp.147–162.

Faulkner, A., Kent, J., Geesink, I. and Fitzpatrick, D. (2003) 'Human tissue-engineered products – drugs or devices? Tackling the regulatory vacuum', *British Medical Journal*, Vol. 326, pp.1159–1160.

Freeman, C. (1995) 'The national systems of innovation in historical perspective', *Cambridge Journal of Economics*, Vol. 19, pp.5–24.

Henderson, J.V. (1986) 'The efficiency of resource usage and city size', *Journal of Urban Economics*, Vol. 19, pp.47–70.

Henderson, R., Orsenigo, L. and Pisano, G. (1999) 'The pharmaceutical industry and the revolution in molecular biology: exploring the interactions between scientific, institutional and organizational change', in D. Mowery and R. Nelson (Eds). *The Sources of Industrial Advantages*, Cambridge: Cambridge University Press, pp.267–311.

Klepper, S. (2002) 'The capabilities of new firms and the evolution of the US automobile industry', *Industrial and Corporate Change*, Vol. 11, pp.645–666.

Klepper, S. and Simons, K. (1997) 'Technological extinctions of industrial firms: an inquiry into their nature and causes', *Industrial and Corporate Change*, Vol. 6, No. 2, pp.379–460.

Krugman, P. (1991) 'Increasing returns and economic geography', *The Journal of Political Economy*, Vol. 99, pp.483–499.

Maskell, P. (2001) 'Towards a knowledge-based theory of the geographical cluster', *Industrial and Corporate Change*, Vol. 10, No. 4, pp.921–944.

Nelson, R.R. and Winter, S. (1982) *An Evolutionary Theory of Economic Change*, Cambridge, MA: The Belknap Press of Harvard University Press.

Nightingale, P. and Mahdi, S. (2006) 'The evolution of pharmaceutical innovation', in G. Dosi and M. Mazzucato (Eds). Knowledge Accumulation and Industry Evolution. The Case of Pharma-Biotech, Cambridge: Cambridge University Press, pp.73–111.

Nightingale, P. and Martin, P. (2004) 'The myth of the biotech revolution', *Trends in Biotechnology*, Vol. 22, No. 11, pp.564–569.

Orsenigo, L. (2006) 'Clusters and clustering in biotechnology: stylised facts, issues and theories. From clusters to network structures and their dynamics', in P. Braunerhjelm and M. Feldman (Eds). Cluster Genesis, Oxford: Oxford University Press, pp.195–218.

Orsenigo, L., Pammolli, F. and Riccaboni, M. (2001) 'Technological change and network dynamics. The case of the bio-pharmaceutical industry', *Research Policy*, Vol. 30, pp.485–508.

Pisano, G.P. (2006) *Science Business: The Promise, the Reality and the Future of Biotech*, Cambridge, MA: Harvard Business School University Press.

Tait, J. (2007) 'Systemic interactions in life science innovation', *Technology Analysis and Strategic Management*, Vol. 19, No. 3, pp.257–277.

Tait, J., Chataway, J., Lyall, C. and Wield, D. (2006) 'Governance, policy and industry strategies: pharmaceuticals and agro-biotechnology', in G. Dosi and M. Mazzucato (Eds). Knowledge Accumulation and Industry Evolution. The Case of Pharma-Biotech, Cambridge: Cambridge University Press, pp.378–401.

Thomas, L.G. (1994) 'Implicit industrial policy: the triumph of Britain and the failure of France in Global Pharmaceuticals', *Industrial and Corporate Change*, Vol. 3, No. 2, pp.451–489.

Wong, J.F. (2005) 'Is biotech in the midst of a fifty year cycle?' *Genetic Engineering News*, Vol. 25, No. 5, p.60.