# Biotechnology Clusters in the U.K.: Lessons from Localisation in the Commercialisation of Science

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ABSTRACT. Today, U.S. biotechnology firms dominate the growing therapeutics and diagnostics sectors despite most of the key discoveries being made by European, and especially U.K. scientists. Lessons have been learned about the economic importance of commercialisation of bioscience. Within Europe, the U.K. is the leading challenger of U.S. hegemony in biotechnology exploitation. Knowledge-driven clusters of start-ups and established smaller and medium-sized businesses have developed in Cambridge and Oxford along with nascent agglomerations in Surrey and Scotland. They are responsible for the turnaround. As in the U.S., intimate links with large pharmaceutical firms and publicly-funded research centres are key to spin-out businesses, suggesting a generic "new economy" model. The specific problem at present is scale and the need to make up ten years lost ground. But the evidence is there that the U.K. is taking up the competitive challenge.

## 1. Introduction

It is widely thought that the U.K. is Europe's leading biotechnology economy despite lagging the position of the U.S. very markedly. This tends to be argued in terms of U.K. ownership of large pharmaceutical companies, the strength of the science base, and the possession of some 270 specialist biotechnology firms, compared to, say, Germany's 220 and France's 140 (Ernst & Young, 1999). However, if we look at the position in terms of market penetration of U.K.-originated therapeutic products derived from biotechnology, the position is little better, and may indeed be worse than that of Germany. In this paper an effort is made to explain this position but also explore the rapid, if belated growth of the U.K. biotechnology sector. It will be shown that much of the rise in commercialisation of biotechnology is at the hands of small start-up and spin-out companies originating in the U.K. science base. As in the U.S. and even more recently in Germany, these firms operate in localised business clusters (Audretsch, 1998; Audretsch and Feldman, 1996; Jaffe et al., 1993). This is interesting, not least due to regulatory variation among these countries. It is argued that biotechnology is unusual in being heavily dependent everywhere upon major public funding of basic scientific research, in turn giving rise to spin-out activity in geographical proximity to universities, research hospitals and public research laboratories. Europe is beginning to emulate U.S. practice in this respect.

To analyse the gap between U.S. cluster formation in biotechnology and that in the U.K., as well as the firm formation which constitutes the clustering phenomenon, we can see how much U.S. spin-out biotechnology products dominate world markets (Swann and Prevezer, 1996; Prevezer, 1999). Even large pharmaceutical firms are less innovative than the "entrepreneurial" sector (Ernst & Young, 1999) in this regard, and this is doubly true for European "big pharma". The slight advantage to Germany over the U.K. was that in 1998 it at least had Boehringer Mannheim's (now Roche, of Switzerland) Reteplase cardiac drug on the market. Contrariwise it is hard to find a single U.K.-originated product derived from recombinant or genetically modified organisms or cells, despite the presence of 53 distinct products on the U.K. market. Even Glaxo's successful Epivir (HIV) product which is in the world top ten selling drugs was developed by Montreal-based BioChem Pharma. It can be seen that basically no U.K. pharmaceutical firms even market biotech-

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nological products in the U.K., that no U.K.-originated biotechnological drugs are on sale in the U.K. and that, at the end of 1999, the U.K. market was completely foreign-dominated. The key question addressed is whether this position (replicated now also in Germany) is likely to be changed in the near future.

## 2. Market penetration in the U.K.

The data on origination of biotechnology drugs available in the U.K. market on which the following text is based are provided through the U.K. Bioindustry Association by the U.K. Department of Health Medicines Control Agency. A great deal of sleuthing has to be performed with the MCA data since they depend on the data of the European Agency for the Evaluation of Medical Products who, in granting market authorisations, do not always provide full details of the manufacturer of the active substance. They further note that details of the manufacturer of the active substance are also confidential. What is not confidential is the licence holder details, but that information is very misleading when seeking the product originator. So, an attempt has been made to penetrate the veil of confidentiality by reference to consultancy reports and databases which do note some product originators (e.g. Schitag, Ernst & Young, 1998; Ernst & Young, 1999; BioCentury, 1998) and biosciences directories which in giving local firm profiles sometimes list also the drugs they have originated, described by brand-name. Of the 53 approved drugs, 48 have been traced. Further research is then presented on the likelihood of growth in the capability of U.K. biotechnology firms to compete with the U.S. as they develop therapeutic and other products. Many of these are already in the pipeline. The development of biotechnology clusters in the U.K. is central to the strong future prospects for the biotechnology sector to lessen the product gap with the U.S.

In Table I, twenty-five of the twenty-eight U.K.-licensed biopharmaceutical products have been traced to the product originator. Of the remaining three, none are marketed by U.K.-owned licence holders; Roche Products, Schering-Plough and Unigene being the marketers in question. We see that market penetration by non-U.K. products is overwhelming and that U.K. giants like Glaxo, SmithKline Beecham (merged in 2000) and Zeneca are not marketing them. The industry is, therefore, highly globalised. Moving on to the twenty-five therapeutic products derived from biotechnology that are sold on the U.K. market by foreign or U.K. firms based in a licence holder country outside the U.K. (e.g. France, The Netherlands, Belgium etc.) we find that origination data can thus far be tracked-down for twenty-three drugs. These are presented in Table II. Here, SmithKline Beecham is active as a marketer, but from its Belgium base. From the analysis the conclusion that no U.K.-originated, biotechnology-derived therapeutic product is currently on sale in the U.K. market is difficult to avoid.

## 3. The future

If the present reveals the U.K. market for biotechnology-derived drugs to be dominated at the end of the twentieth century by products largely originating in U.S. entrepreneurial biotechnology firms where does the challenge for the next century lie? If it is to come from Europe, it seems likely that the fledgling U.K. therapeutic products industry will have a greater impact in the next few years. Let us look, first, at some of the key milestones in the development of biotechnology, since these give a hint of the evolving basic science which is the resource for future commercialisation if exploitation opportunities can be taken.

It is clear from Table III that the U.K. has been a leading location for many of the main research breakthroughs in biotechnology in the second half of the twentieth century. This began with the pioneering work of the U.K./U.S. team of Watson and Crick working at Cambridge's Cavendish Laboratory, supported crucially by Rosalind Franklin's X-ray diffraction results at Wilkin's laboratory in Kings College, London. However, if we look at milestones in commercialisation of biotechnological knowledge, it is the U.S. that takes the early lead. Thus Genentech was set up by recombinant DNA technologist Boyer and venture capitalist Swanson (Kleiner et al.) in 1976. Amgen followed in 1980 and in 1982 Humulin, the first genetically-produced human insulin, developed by Genentech with Eli Lilly, was given U.S. Food and Drug Administration approval. The

TABLE I
Approved biotechnology drugs in the U.K. (U.K.-licensed)

| Product | Developer | Marketer | Active substance | Marketer home base |
|---|---|---|---|---|
| Zenapax | Protein Design Labs Inc. (CA) | Roche Registration Ltd. (U.K.) | Daclizumab | Switzerland |
| Recormon | Genetics Inst. (MA) | Boehringer M. (U.K.) | Epoetin beta | Germany |
| Recombinate | Genetics Inst. (MA) | Baxter Healthcare Ltd. (U.K.) | Factor VIII | U.S.A. |
| Neupogen | Amgen (CA) | Roche Products Ltd. (U.K.) | Filgrastim | Switzerland |
| Gonal F | Ares-Serono (Italy/Switzerland) | Ares-Serono (Europe) Ltd. (U.K.) | Hormone alpha | Switzerland* |
| Vaqta | Merck (U.S.) | Pasteur-Merieux MSD Ltd. (U.K.) | Hepatitis A | France |
| HIB-Vax | Connaught Labs (Canada) | Pasteur-Merieux MSD Ltd. (U.K.) | Hepatitis B | France |
| Humulin | Genentech (CA) | Lilly Industries Ltd. (U.K.) | Human Insulin | U.S.A. |
| Humaject | Genentech (CA) | Lilly Industries Ltd. (U.K.) | Human Insulin | U.S.A. |
| Liprolog | Eli Lilly (U.S.) | Lilly Industries Ltd. (U.K.) | Insulin Lispro | U.S.A. |
| Insulatard | Novo Nordisk (Denmark) | Novo Nordisk Pharma Ltd. (U.K.) | Human Insulin | Denmark |
| Penmix | Biogen (MA) | Novo Nordisk Pharma Ltd. (U.K.) | Human Insulin | Denmark |
| Mixtard | Biogen (MA) | Novo Nordisk Pharma Ltd. (U.K.) | Human Insulin | Denmark |
| Actrapid | Biogen (MA) | Novo Nordisk Pharma Ltd. (U.K.) | Human Insulin | Denmark |
| Roferon | Genentech (CA) | Roche Products Ltd. (U.K.) | Interferon alpha2a | Switzerland |
| Intron-A | Biogen (MA) | Schering-Plough Ltd. (U.K.) | Interferon alpha2b | U.S.A. |
| Rebif | Ares-Serono (Italy/Switzerland) | Ares-Serono (Europe) Ltd. (U.K.) | Inteferon beta 1a | Switzerland |
| Immukin | Genentech (CA) | Boehringer Ingelheim Ltd. (U.K.) | Interferon gamma1b | Germany |
| Granocyte | Merrell Dow/Immunex (U.S.) | Chugai Pharma (U.K.) Ltd. | Lenograstim | Japan |
| Leucomax | Genetics Institute (MA) | Schering-Plough Ltd. (U.K.) | Molgramostin | U.S.A. |
| Kogenate | Miles Labs/Genentech(CA) | Bayer plc (U.K.) | Factor VIII | Germany |
| Genotropin | Genentech (U.S.) | Pharmacia Labs Ltd. (U.K.) | Growth Hormone | Sweden/U.S.A. |
| Humatrope | Genentech (CA) | Lilly Industries Ltd. (U.K.) | Growth Hormone | U.S.A. |
| Norditropin | Genentech (CA) | Novo Nordisk Pharma Ltd. (U.K.) | Growth Hormone | Denmark |
| Saizen | Serono (Italy/Switzerland) | Serono Laboratories (U.K.) Ltd. | Growth Hormone | Switzerland |

*Source:* U.K. Medicines Control Agency, 1999.
* Serono, Cambridge MA is noted as the originator of this product in Massachusetts Biotechnology Council, 1998.

Massachusetts biotechnology leading firms were founded as follows: Biogen (1978), Genetics Institute (1980) and Genzyme (1981). Qiagen Germany's leading entrepreneurial biotechnology firm was established in 1984, and the U.K.'s first firm, Celltech, was founded with Labour government funding in 1979. Celltech recently merged with Chiroscience, one of the U.K.'s leading biotechnology firms. In a possibly significant reversal of historic practice, the two recently acquired Medeva, a pharmaceuticals firm.

During the 1990s the commercialisation climate changed in the U.K. and Germany and there has been an increase in the number of biotechnology firms, especially in the health care and biopharmaceuticals sectors, with a slower rate of growth in agro-food biotechnology and bioenvironmental technology businesses. Growth in the number and scale of U.K. biotechnology firms occurred earlier than in Germany, for example. In the latter case, a serious push to break the commercialisation logjam occurred in the late 1990s in the wake of the Federal Ministry of Science, Education, Research and Technology's (BMBF) BioRegio competition (Giesecke, 1999; Dohse, 1999, 2000). Prospects for the emergence of independent biotechnology firms are explored below, but for the moment, given the future perspective in this section, the focus is on developments in the pipeline regarding firms and therapeutic products in Europe as a whole. This inevitably draws particular attention to the U.K., as Europe's leading biotechnology product development economy. There are a number of ways of engaging in such a prospective look at the sector. We can look first at firm-specific information in terms of market capitalization, turnover, profit and loss, R&D expenditure and employees. We can then look at therapeutic products by stage in the pipeline regarding clinical trials

TABLE II
Approved biotechnology drugs in the U.K. (EU country-licensed)

| Product | Developer | Marketer | Active substance | Licence holder country |
|---|---|---|---|---|
| Proleukin | Chiron (CA) | Chiron B.V. | Aldesleukin | Netherlands |
| Bioclate | Armour Pharma(U.S.) | Centeon Pharma GmbH | Antihaemophilia | Germany |
| Revasc | Ciba (Switzerland) | Rhone-Poulenc-Rorer S.A. | Desirudin | France |
| Neorecormon | Genetics Inst. (MA) | Boehringer Mannheim GmbH | Epoetin beta | Germany |
| Recormon | Genetics Inst. (MA) | Boehringer Mannheim GmbH | Epoetin beta | Germany |
| Puregon | N.V. Organon (Netherlands) | N.V. Organon | Follitropin beta | Netherlands |
| Twinrix | Chiron (CA) | SK Beecham S.A. | Hepatitis B | Belgium |
| Infanrix | Chiron (CA) | SK Beecham S.A. | Hepatitis B | Belgium |
| Tritanrix | Chiron (CA) | SK Beecham S.A. | Hepatitis B | Belgium |
| Primavax | Pasteur Merieux (France) | Pasteur Merieux MSD | Hepatitis B | France |
| Benefix | Genetics Inst (MA) | Genetics Inst. of Europe B.V. | Factor VIII | Germany |
| Cerezyme | Genzyme (MA) | Genzyme B.V. | Imiglucerase | Netherlands |
| Protophane | Novo Nordisk (Denmark) | Novo Nordisk A/S | Human Insulin | Denmark |
| Remicade | Centocor Inc. (CA) | Centocor Europe B.V. | Infliximab | Netherlands |
| Humalog | Genentech (U.S.A.) | Eli Lilly Nederland B.V. | Insulin lispro | Netherlands |
| Procomvax | Pasteur Merieux (F) | Pasteur Merieux MSD | Hepatitis B | France |
| Avonex | Biogen (MA) | Biogen S.A. | Interferon beta 1a | France |
| Betaferon | Chiron (CA) | Schering A.G. | Interferon beta 1b | Germany |
| Refludan | Merrel Dow (U.S.A.) | Hoechst Marion Roussel | Lepirudin | Germany |
| Rofacto | Genetics Inst. (MA) | Genetics Inst. of Europe B.V. | Factor VIII | Germany |
| Helixate | Miles Labs/Genentech (CA) | Bayer A.G. | Factor VIII | Germany |
| Triacelluvax | Chiron (CA) | Chiron s.p.a. | Pertussis toxin | Italy |
| Novoseven | Biogen (MA) | Novo Nordisk A/S | Factor VIIA | Denmark |

*Source:* U.K. Medicines Control Agency, 1999.

TABLE III
Selected key biotechnology innovations

| Date | Innovation | Scientists | Country |
|---|---|---|---|
| 1953 | DNA Structure | Watson/Crick | U.K. |
| 1974 | In vitro recombinant DNA | Cohen/Boyer | U.S. |
| 1975 | Monoclonal Antibodies | Milstein/Kohler | U.K. |
| 1977 | DNA Sequencing | Sanger et al. | U.K. |
| 1978 | Polymerase chain reaction | Mullis | U.S. |
| 1979 | p53 Cancer gene | Lane | U.K. |
| 1982 | Cascade superfusion bioassay | Vane | U.K. |
| 1985 | DNA Profiling | Jeffreys | U.K. |
| 1988 | H2 – receptor antagonist | Black | U.K. |
| 1996 | Transgenic sheep | Wilmut | U.K. |
| 1998 | Antibody protein engineering | Winter | U.K. |
| 1998 | Nematode worm sequence | Sulston | U.K. |

*Source:* Schitag, Ernst & Young, 1998; BioIndustry Association, 1999.

and, as appropriate, cross-reference the two sets of indicators.

In Table IV statistics are provided on Europe's top ten performing 'entrepreneurial' biotechnology (pharmaceutical) firms. Three things are of immediate interest. First is the predominance of U.K. firms (60%) in the listing, with only one from each of four other European countries entering the rankings. Second, for all of them, the striking difference between their valuation, in terms of market capitalisation, and their much lower turnover is testimony to the speculative

TABLE IV
Top ten European biotechnology pharmaceutical firms, 1998 ($ million)

| Company | Market capitalisation ($m) | Turnover | Profit/Loss | R&D costs | Employees |
|---|---|---|---|---|---|
| Qiagen (Germany) | 959 | 103 | 12 | 12 | 785 |
| Shire Pharma (U.K.) | 844 | 75 | 6 | 9 | 426 |
| Innogenetics (Netherlands) | 737 | 46 | –14 | 20 | 630 |
| Powderject (U.K.) | 540 | 48 | –7 | 11 | 87 |
| Genset (France) | 522 | 29 | –16 | 37 | 479 |
| Celltech (U.K.) | 480 | 18 | –17 | 33 | 218 |
| Chiroscience (U.K.) | 437 | 40 | –36 | 56 | 302 |
| Neurosearch (Denmark) | 387 | 8 | –6 | 16 | 113 |
| Oxford Asymmetry (U.K.) | 338 | 23 | 4 | 2 | 219 |
| British Biotech (U.K.) | 334 | 1 | 70 | 66 | 445 |

*Source:* BioCentury, 1998; Ernst & Young, 1999.

confidence of stock market investors in the industry. Third, biotechnology has high-value lead firms, the overwhelming majority of whom are making losses not profits. A further feature probably worth noting about these knowledge-intensive businesses is the often high R&D costs per employee ratio most display. Hence, what are such investor expectations based upon? Table V lists the new products in the pipeline and, while some of the firms featuring in Table IV are the origin of these products-in-trial, other smaller firms also enter the scene.

Once again, and bearing in mind these are selected therapeutic products in trial, the dominance of U.K. companies at the various trial stages from pre-clinical to phase 3, which is close to market, is most striking. Eleven of the sixteen firms and twenty-one of the thirty products are U.K.-originated in Ernst & Young's latest list of innovative products expected from European biotechnology-specialist firms. These therapeutic products are subject to exacting preclinical and clinical trails (Phases 1, 2 etc.) and it is this testing process which explains the high level of R&D investment noted in Table IV since this is the stage at which the cash "burn rate" is high, venture capital has accordingly had to be accessed and firms are seeking to enter public markets to recoup the finances invested. Moreover, many such firms have already entered partnership agreements with big pharma companies for the licensing of technologies which, when granted approval, are marketed and distributed by the multinationals, as we have seen. For example, Cantab Pharmaceuticals' two therapeutic vaccines noted in Table V have been licensed to Glaxo Wellcome and SmithKline Beecham, while Transgène licensed its two gene delivery systems to Schering-Plough. Companies such as Cantab Pharmaceuticals, Transgène and the German firm MediGene are thought to be capable of head-to-head competition with U.S. firms in the field of therapeutic vaccines because there is no dominant company globally in this field which seeks to stimulate immune responses to genetic diseases. MediGene has a development partnership with Germany's leading big pharma firm Hoechst Marion Roussel (now merged with Rhone-Poulenc to form Aventis), to advance its tumour vaccination technologies.

If therapeutic vaccines are a relative European strength, the other future growth sector of biochips is primarily led by U.S. diagnostics firms. Biochips aim to miniaturise biological assay processes so that the whole genetic make-up of a particular human being can be analysed simultaneously by the family doctor. Firms such as Affymetrix and Hyseq lead the field although Amersham (U.K.) acquired Molecular Dynamics of the U.S. giving them a globally competitive market position. Biochips link to *functional genomics*, a growth field dealing with the relationships between gene functions and the diagnosis and eventual treatment of human diseases. In 1998 Affymetrix entered partnerships with twelve firms, including bioMérieux (France), Gemini Research (U.K.), Glaxo (U.K.) and Roche (Switzerland) to develop biochips. Gemini is the

TABLE V
Pipeline products from European biotechnology companies, 1998

| Company | Product | Indication | Trials status |
|---|---|---|---|
| British Biotech (U.K.) | BB-10153 | Cardiovascular | Phase 1 |
| | BB-3644 | Cancer treatment | Preclinical |
| Cantab Pharma.(U.K.) | TAGW | Genital warts | Phase 2 |
| | DISC HSV | Genital herpes | Phase 1 |
| Celltech (U.K.) | CDP 571 | Crohn's disease | Phase 2b |
| | CDP 870 | Rheumatoid arthritis | Phase 2 |
| Chiroscience (U.K.) | D2163 | Cancer inhibitor | Phase 1/2 |
| | Dermal Powderject | Anaesthetic | Phase 2 |
| Cortecs (U.K.) | Ulsastat | Ulcer Immunity stimulator | Preclinical |
| | Cellcom | Cancer treatment | Preclinical |
| Flamel (France) | Asacard | Cardiovascular | Phase 2 |
| | Basulin | Diabetes | Preclinical |
| IDM (France) | MAK | Ovarian bladder cancer | Phase 2 |
| | MSC-DC | Cancer vaccine | Preclinical |
| Innogenetics (Netherlands) | Toleri Mab | Prevent organ rejection | Preclinical |
| Peptide Therapeutics (U.K.) | Tolerizing peptide | Hay fever | Phase 2 |
| | HSP immunotherapeutic | Rheumatoid arthritis | Preclinical |
| Phytopharm (U.K.) | P54 | Colonic cancer treatment | Phase 2a |
| Powderject (U.K.) | Alprodastil | Erectile dysfunction | Phase 1 |
| | PJ2204 | Acute migraine | Preclinical |
| Neurosearch (Netherlands) | NS 2710 | Anxiety disorders | Phase 2 |
| | NS 2330 | Dementia | Phase 2 |
| Scotia Holdings (U.K.) | Epakex | Cancer treatment | Phase 2 |
| | Meglumine-GLA | Bladder cancer | Phase 1 |
| Shire Pharma. (U.K.) | TriClimactol | Hormone replacement therapy | Phase 3 |
| | Galantamine | Chronic fatigue syndrome | Phase 2 |
| Transgène (France) | Adenovirus-CFTR | Cystic fibrosis | Phase 1 |
| | Adenovirus-IFN | Immune enhancement | Preclinical |
| Vanguard Medica (U.K.) | VML 530 | Asthma | Phase 1 |
| | VML 600 | Hepatitis C | Preclinical |

*Source:* BioCentury, 1998; Ernst & Young, 1999.

U.K.'s first clinical genomics firm. Amersham's purchase of Molecular Dynamics also means that it has access to the Genetic Analysis Technology Consortium involving leading biochip firm Affymetrix. Hence, the technological lead of the U.S. in biochips is likely to narrow considerably with European firms more actively involved. From the point of view of these two leading technology areas of the future, it seems likely that Europe, and most particularly the U.K., shows significant signs of levelling up compared to the position in the 1980s from when U.S. firms dominated biotechnology applications and products.

This is underlined by the emergence of many new spin-out firms from leading U.K. research centres. In Cambridge, Pharmagene and Hexagen are both involved in functional genomics, seeking therapeutic treatments from genomics information. Brax, Gemini and Chiroscience are also operating in fields using genomics data, the last-named having acquired Darwin Molecular of Seattle to boost its genomics capabilities. Hexagen was also acquired in 1998 by U.S. genomics specialist Incyte Pharmaceuticals, joining Incyte's new pharmacogenetics division Incyte Genetics. As well as these Cambridge-focused firms, there are important growth firms evolving from genomics research in Oxford, such as Oxagen, Oxford Glycosciences, Oxford Molecular and Oxford Asymmetry. Firms such as Oxford Asymmetry and

Oxford Glycosciences possess bioinformatics libraries that are of major value to large pharmaceutical firms. Thus Bayer and Dow AgroSciences both signed deals with Oxford Asymmetry to access drug discovery information from its libraries, while Oxford Glycosciences contracted similarly for access to its proteomics library.

The existence of such firms, formed to take advantage commercially of the major public and charitable investments that have been placed in genomics research both at Oxford and, especially, Cambridge, remind us of the highly localised but also simultaneously globalised relationships among firms that characterise the cutting edge of biotechnology research and commercialisation. According to Mihell et al. (1997) Cambridge has some seventy-six biotechnology firms and research organizations while Oxford has forty companies directly involved in biotechnology. Another agglomeration, of some thirty-seven firms, is centred upon Surrey, to the south of London, with yet another concentration of over fifty in Scotland. However, research conducted by the U.K. Department of Trade and Industry (DTI, 1999a) differentiated Surrey from Cambridge and Oxford. The last two displayed the characteristics of clusters, whereas Surrey and Scotland did not and Scotland was seen as a latent cluster. The main rationale for this judgement about Surrey (but not Scotland) was the relative absence of local linkage to the science base and systematic start-up and spin-out activity centred on established, university-based technology-licensing, transfer and enterprise support within science park and incubator settings. Both Cambridge and Oxford display these specialist characteristics in close proximity to the science base, something Prevezer (1995) highlights as the key characteristic also defining successful U.S. biotechnology clusters.

## 4. Globalization and clustering: the new balance of power

We have seen how smaller new firms from the U.S., expert in the application of basic science findings often discovered elsewhere, notably the U.K., became dominant sources of commercialisation of biotechnology. They remain dependent upon big pharma companies for the finance to produce, market and distribute the drug treatments eventually emanating from the lengthy gestation process typical of many biotechnology products (Powell et al., 1996). The "absorptive capacity" of big pharma regarding this new industry was insufficient to enable it to displace the Genentechs and Amgens from their position of primary innovator, though many have retained sufficient of this capability to understand the meaning of cutting edge research if not to replicate it (Cohen and Levinthal, 1990). The reason for this is that the core knowledge was and has remained produced in university and other public research laboratories more than in the R&D labs of big pharma itself. Such was the relative strength of public labs over private in this respect that the initial strategies of firms such as those noted as early movers in California and Massachusetts were to become Fully Integrated Pharmaceutical Companies (FIPCOs) and thus to challenge the predominant pharmaceutical firms, rather as has occurred with Intel and Microsoft in relation to IBM and others in IT. However, today this is not the case for a number of reasons. First, firms attempting the FIPCO strategy failed to achieve it because barriers to entry were relatively low for competitors focusing more on a stage or stages in the development of a particular drug. Second, the cost of drug development in biotechnology is extremely high. Third, the time taken through the research and trialling until final approval stages of a new drug is enormously long. Fourth, the risk that a trialled drug will not in fact prove itself workable or effective is very high, perhaps only one in ten proving successful. Finally, the industry is turbulent, with many emerging technologies and a reasonably supportive environment for new, niche strategies by emergent small firms.

While globalisation and local clustering are key characteristics of biotechnology, a question arises as to whether the fact that clustering developed quickly in the U.S.A., followed a decade later in the U.K., but being induced only with the subsidies of federal and regional governments in, for example Germany, signifies crucial competitive advantage for the first two from distinctive national business and regulatory systems. This is a large question, demanding full-length analysis and interpretation. An initial effort to start such analysis is that of Casper et al. (1999), comparing U.S. and German systems for software and

biotechnology. It is hard to disagree with their view that on three key counts the U.S. has the more liberal business environment. In Germany scientific labour is regulated in ways that hinder mobility, corporate governance rules made stock options illegal until 1998, and banks dominate a (conservative) investment environment. So private venture capital has been traditionally under-represented, spin-off firms hard to launch and entrepreneurship not a highly-valued career option. The last sentence could almost describe the U.K. up to perhaps a decade ago. Stock options, while not illegal, are only in 2000 seeing tax thresholds lowered, a government inquiry into the low amounts of venture capital invested by pension funds was launched in the same year and entrepreneurship initiatives comparable to those already launched in Germany have been part of official policy, particularly under Labour since 1997. Nevertheless, the general business climate in the U.K. seems to be becoming more favourable to the commercialisation of science (DTI, 1999b). The processes involved are also more market-led, albeit often with government urging, than public-sector-led with banking (including venture capital) and big pharma co-funding, which is the current German model. Despite this, clusters have begun to form in a number of German regions, and judgement as to their future robustness in competitive world markets is awaited with interest.

Thus current and past industry dynamics point strongly to a continuation of the importance of a cluster model of business co-ordination. Opportunities associated with commercialisation of genomics information have strengthened rather than weakened the salience of this model by adding new phases to the drug discovery process, into which specific niche-oriented firms can fit. Hence, firms focus on developing "*platform technologies*", which accelerate the prospects of drug discovery. In biopharmaceuticals, these link core genomics technologies such as genome analysis, bioinformatics, protein analysis and functional genomics to diagnostics and therapeutic products via such technologies as biosensors, DNA arrays, biochips, monoclonal antibodies and polymerase chain reaction, amongst others. The largest of these companies are U.S. in origin, such as Millennium, Myriad Genetics, Axys, Incyte, Genome Therapeutics and Human Genome Sciences. Millennium and Monsanto have formed a partnership, as even more so did Hexagen (U.K.) acquired by Incyte (U.S.). German firms like MophoSys (Pharmacia-Upjohn, Swedish/U.S.) and Evotec Biosystems (Novartis of Switzerland and SmithKline Beecham of the U.K.) have also become involved in partnerships with foreign big pharma. Thus we see that entrepreneurial biotechnology firms are, if anything, strengthening their control over the product development process while courting big pharma for licensing and downstream marketing and distribution. Proximity to the science base and capability to transform rapidly potential knowledge into products remain defining characteristics of biotechnology. The clustering model which predominated early in the U.S.A., has developed more recently in the U.K., notably at Cambridge and Oxford.

## 5. Cambridge, Oxford and Surrey

U.K. commercial biotechnology effectively started with the establishment of Celltech in 1979. High-level concern at the failure of the Medical Research Council's Molecular Biology Laboratory to patent their discovery of monoclonal antibodies, and efforts by the Callaghan government to try to remedy the U.K.'s lagging position in new, high technology markets led to the National Enterprise Board and MRC supporting the formation of a state-funded firm. Intended to be set up in Cambridge in proximity to the science base, property availability resulted in Celltech setting up in Slough, west London where it remains. In 1999 it merged with Chiroscience, one unit of the merger to be known as Celsis. Subsequently Celltech-Chiroscience acquired pharmaceuticals firm Medeva, the first such purchase by a biotechnology company, and a variation upon the FIPCO ambition.

This marks a resurgence of confidence in the sector following three years of low stock market expectations, largely contingent on the slump in fortunes of British Biotech (see below). Added to this, public concern about the possible health effects of Genetically Modified Organisms and opposition to secretive governmental processes of regulating trials by industry leaders like Monsanto reinforced investor reluctance. However, between mid-1999 and the first quarter of 2000 the U.K.

biotechnology sector grew nearly four times faster than the Financial Times Stock Exchange (FTSE) all-share index, echoing a fivefold increase in the equivalent Standard & Poor composite index in the U.S. In the U.K. Cambridge Antibody Technology (see below) an industry 'lighthouse' company saw its share price rise from 165 pence to £42 and a value of £100 ($160) million. Celltech-Chiroscience-Medeva had a second-quarter-2000 capitalisation of £2.8 billion, two strong drug prospects in Humicade (antibody for Crohn's disease) and CDP 870 (rheumatoid arthritis), and two more in development. Crucially for a biotechnology firm, it is in sustained profit and capitalised as one of the U.K.'s top 100 (FTSE index) companies. Though not in the same league as Californian pioneer biotechnology firm Amgen, which, at $70 billion became, in early 2000, worth more than Eli Lilly, Schering-Plough and (before merger with Glaxo) SmithKline Beecham, nevertheless U.K. firms are beginning to develop scale and recover investor confidence as therapeutic products get closer to the market. In the following section accounts are provided of the clustering characteristics that underpin the resurgent U.K. biotechnology sector.

### *Oxford*

The U.K.'s most notorious indigenous biotechnology firm, British Biotechnology was a spin out from the American firm Searle (part of Monsanto) of High Wycombe (near Oxford), when the latter closed U.K. operations in 1985. Two research directors established British Biotech and by 1992 it had become the U.K.'s first publicly floated biotechnology company. Its site at Cowley is close to other Oxford-based biotechnology ventures such as Oxford Glycosciences, Oxford Molecular and Xenova. In 1997 British Biotech was Europe's largest biotechnology company in terms of market capitalisation and R&D costs, and second to Qiagen of Germany in employment, with 454 employees. Then the company suffered a $2 million stock market decline because of delays in gaining approval for its two leading products. Confidence was badly hit everywhere in Europe by this setback to its leading company. Subsequent disclosures of potentially fraudulent practices in stoking up the stock market price did not help. Celltech also received a big setback with Bayer's announcement of withdrawal from support for its septic shock treatment, leading to a 48% price drop. Investor confidence was further damaged by poor drug trial results from Scotia Holdings and Stanford Rook. The British Biotech clinical trials head, who was fired for questioning the effectiveness of the firm's cancer treatment in public, moved to Oxford Gene Technology (OGT) Operations, a commercial offshoot of Oxford University biochemist Ed Southern's pioneering research in DNA biochip technology. OGT was, in 1999 in legal dispute with Affymetrix over the invention of the DNA biochip, which the American firm has patented. OGT is a spin-out from Oxford University which retains a 10% stake in the firm, set up in 1995 to manage income from Southern's DNA microarray patents.

Other Oxford firms of significance in biotechnology include Oxford University spin-out Oxford GlycoSciences, the world's leading proteomics firm, now partnered with Incyte Pharmaceuticals of California, Oxagen (functional genomics) based in nearby Abingdon, and therapeutics company Oxford Molecular. Other firms in the extended Oxford cluster, which is aligned down the A34 highway corridor, are near Abingdon and Didcot on the Milton Science Park and include Prolifix, a cell cycle control therapeutics firm, Oxford Asymmetry in bioinformatics and Cozart BioSciences (immunodiagnostics). A number of newer firms are located at Oxford Science Park, including Progenica (diagnostics), Oxford Therapeutics (drug development), Oxford BioResearch, Kymed (biopharmaceuticals) and Evolutec (drug discovery). Other centres such as the Medawar Centre and Abingdon Science Park also house biotechnology firms.

The Institute of Molecular Medicine at the John Radcliffe Hospital, Oxford (part of Oxford University's Clinical School) is a leading research institute which spins out new firms, notably specialising in oncology and AIDS/hepatitis vaccines, in partnership with Isis, the Oxford University technology licensing and spin-out support organization, private investors and venture capitalists. Oxagen in Abingdon is a recent spin-out from the Wellcome Trust Centre for Human Genetics in Oxford, and Prolifix was spun out from the Medical Research Councils' National

Institute for Medical Research in London. Yamanouchi Research Institute is the first privately-funded biotechnology research institute to be established in the area (1990). In 1999, Oxfordshire BioScience, a network association for the industry was established. Oxford has some 50 biotechnology firms and 200 supply, service or intermediary firms and organizations. It has most of the features of a cluster, though still relatively small, including rising costs of industrial and domestic property, congestion and shortages of venture or other kinds of investment capital (partly caused by the negative British Biotech effect upon investor confidence). In a study by Mihell et al. (1997) it is shown that of 40 biotechnology firms identified in 1995 (50 in 1999), nine out of twelve interviewed were spun out from the university or other public research base, and all firms interviewed had grown swiftly in employment and revenues in the previous five years. Collaboration among local firms and with both the local science base and more distant big pharma are central to firm strategy, though local networking between firms was not as developed as the other links, signifying the comparative immaturity of the cluster. At the time of their survey, in 1996, 2,200 were employed in the 40 firms identified, and new firms were forming at a rate of three to four per year.

### *Cambridge*

Cambridge's core biotechnology industry consists of no less than fifty firms and the broader cluster (venture capitalists, patent lawyers etc.) probably consists of not much more than 200 firms, including the core biotechnology firms. The growth in number of biopharmaceutical firms was from one to twenty-three over the 1984–1997 period, an average of just under two per year, but the rate was four per year in the last two years of that period. Equipment firms grew from four to twelve 1984–1997, and diagnostics firms from two to eight. Table VI(a) shows the breakdown of technology-based companies in Cambridgeshire, while Table VI(b) shows that for support services. Key firms include Cambridge Antibody Technologies, one of twelve spin-outs from the Molecular Biology Laboratory, Chiroscience, a start-up originally based at the Babraham incubator (see below), Cantab Pharmaceutical, Brax Genomics, Churchill Applied Biotechnology and American offshoots Chiron and Amgen. Many of the U.K. firms originated in Cambridge research laboratories and retain close links with them.

The infrastructure support for biotechnology in and around Cambridge is impressive, much of it deriving from the university and hospital research facilities. The Laboratory of Molecular Biology at Addenbrookes Hospital, funded by the Medical Research Council; Cambridge University's Institute of Biotechnology, Department of Genetics and Centre for Protein Engineering; the Babraham Institute and Sanger Institute with their emphasis on functional genomics research and the Babraham and St. John's incubators for biotechnology start-ups and commercialisation, are all globally-recognised facilities, particularly in biopharmaceuticals. However, in the Eastern region are also located important research institutes in the "green bio" field of agricultural and food biotechnology, such as the Institute for Food Research, John Innes Centre, Institute of Arable Crop Research and National Institute of Arable Botany.

TABLE VI
Shares of biotechnology and services functions

| (a) Biotechnology firm distribution | | (b) Biotechnology services distribution | |
|---|---|---|---|
| Biopharmaceuticals | 41% | Sales and marketing | 29% |
| Instrumentation | 20% | Management consulting | 23% |
| Agro-food bio | 17% | Corporate accounting | 15% |
| Diagnostics | 11% | Venture capital | 15% |
| Reagents/Chemicals | 7% | Legal and patents | 8% |
| Energy | 4% | Business incubation | 10% |

*Source:* ERBI (Eastern Region Biotechnology Initiative), 1999.

Thus in research and commercialisation terms, Cambridge is well-placed in biopharmacuticals; and with respect to basic and applied research, but perhaps less so commercialisation, agro-food biotechnology also.

Within a 25-mile radius of Cambridgeshire are found many of the specialist biopharmaceutical firms with which commercialisation development by smaller start-ups and R&D by research institutes must be co-financed. Firms like Glaxo Wellcome, SmithKline Beecham, Merck, Rhone-Poulenc Rorer, Hoechst Pharmaceuticals in the "big pharma" category are represented, and in the specialist biopharmaceutical sector: Amgen, Napp, Genzyme and Bioglan *inter alia*. Thus on another of the criteria for successful cluster development, namely access within reasonable proximity to large customer and funding partner firms, Cambridge is, again, fortuitously positioned.

Finally, with respect to "agro-food bio", Rhone-Poulenc, Agrevo, Dupont, Unilever and Ciba are situated in reasonably close proximity to Cambridge. Hence the prospects for linkage, though more occluded by public concerns about Genetically Modified Organisms than in the case of health-related biotechnology, are nevertheless propitious in locational terms.

Cambridge is relatively well-blessed with science and technology parks, though the demand for further space is significant. At least eight of the afore mentioned "biopharmaceuticals including vaccines" firms are located on Cambridge Science Park itself. St. John's Innovation Centre, Babraham Bioincubator, Granta Park, the Bioscience Innovation Centre and Hinxton Science Park are all recently completed, under construction, or under planning review. Most of the newer developments are taking place within short commuting distance of Cambridge itself, on or near main road axes like the M11, A11, A10 and A14. This is evidence of the importance of *access* for research application firms to centres of basic research, reinforcing also the point that not everything concerning biotechnology must occur "on the head of a pin" in Cambridge city itself.

The final, important, feature of the biotechnology landscape in Cambridge and the surrounding Eastern Region is the presence of both informal and formal networking between firms and research or service organizations and amongst firms themselves. Cambridge Network Ltd. was set up in March 1998 to formalise linkages between business and the research community, connecting both from local to global networks in a systematic way. It is mostly IT-focused, though some of this spills over into biotechnology, given its demand for IT equipment and opportunities for IT delivered patient and clinician services through, for example, telemedicine. Of more direct relevance to the biotechnology community are the activities of the Eastern Region Biotechnology Initiative (ERBI). This biotechnology association is the main regional network with formal responsibilities for newsletter, organizing network meetings, running an international conference, website, sourcebook and database on the bioscience industry, providing aftercare services for bio businesses, making intra- and international links (e.g. Oxford, Cambridge, MA., San Diego), organizing common purchasing, business planning seminars, and government and grant-related interactions for firms.

### *Surrey*

Moving to Surrey, this county contains an agglomeration of some 37 biotechnology firms, according to Mihell et al. (1997), but differs from Cambridge and Oxford in having a great variety of types of firms and relatively few biotechnology research centres. Moreover, there is little interaction between firms in the locale, despite the existence of Southern BioScience, a regional industry association. In 1995 there were some thirty-seven "entrepreneurial" biotechnology firms and related organizations in Surrey. Unpublished figures from the U.K. Department of Trade and Industry note some 120 of all sizes between Surrey and Kent in 1998. Pharmaceutical firms of multinational status such as Pfizer, Rhône Poulenc Rorer and Eli Lilly are found across the two counties, but most firms are SMEs. Despite this, start-up activity has been less noticeable than at Cambridge or Oxford, partly because, despite there being a large number of universities in the wider regional setting, few if any have cutting-edge biotechnological research or pronounced commercialisation strategies. Southern Bioscience, the regional industry association, had assisted eleven new enterprises in

biotechnology by 1999. One bioincubator only exists in the region, at Sittingbourne in Kent where there is a Research Centre on a former Shell plc property. Surrey Research Park has no dedicated "wet lab" space available. Poor availability of suitable premises was cited as a growth barrier in a Southern Bioscience study of the local industry. Other barriers noted were funding gaps, skills weaknesses and poor communication between industry and academia. Moreover, strong networking has been directed outside rather than inside the region, and the regional industry association itself recognises the absence of cluster-like characteristics such as those enjoyed in Oxford and Cambridge.

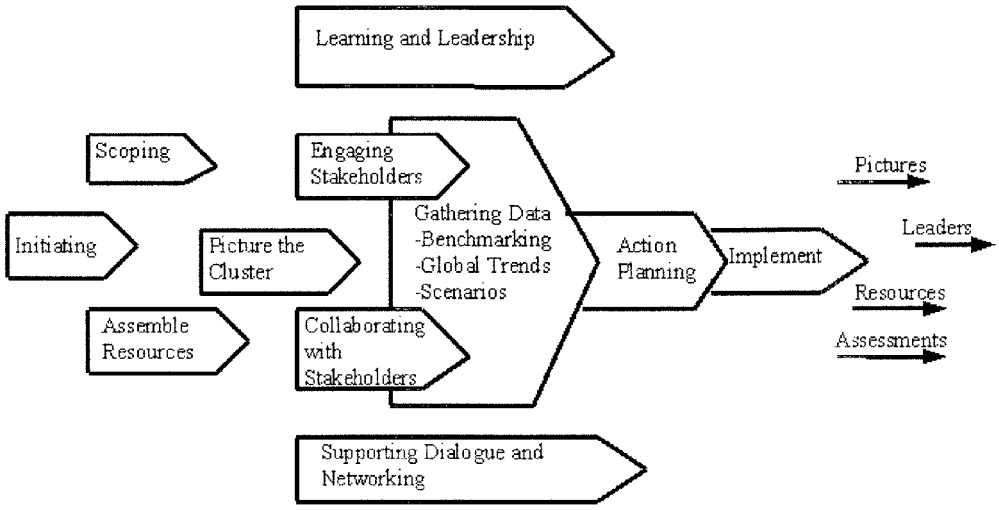
An exemplar of that firm type is Vanguard Medica, a leading drug development firm originating in Surrey, accessing early stage compounds and commercialising them. Frovatriptan is one of Vanguard's successful products for treating acute migraine. Partnerships with academia are directed towards London, Scotland, Europe and the U.S., and collaborating companies include Abbott, Roche and 3M Pharmaceutical. Biocompatibles is a user of biotechnology in its core products, ranging from contact lenses to "stents" (biomedical devices) using polymer synthesis to prevent protein build-up. The company, in interview, said that the Surrey biotechnology industry did not constitute a cluster because of poor linkage with local universities, absence of firms for local outsourcing and testing and the fact that firms have little in common around which to build partnerships. Microgen is a diagnostics firm which conducts environmental and food health monitoring, but has scarcely any local inter-firm links, sources technology from the U.S., where it was once acquired by Centocor, the U.S. biopharmaceuticals firm, before being spun back out into private ownership in 1994. The view in the firm was that it was not part of a cluster, and in this respect there was remarkable unanimity with the other two firms profiled here. Hence, without further labouring the point, the key absence of strong local linkages to knowledge centres, supply chains or horizontally to other biotechnology firms, despite the presence of a regional industry association, points to the absence of clustering despite the presence of considerable industry agglomeration. Nevertheless, biotechnology firms in this area have prospered, demonstrating the importance of global networking even in the absence of the proximate hard and soft infrastructures of the localised, systemic innovation capabilities offered by clusters (Porter, 1998).

### *Scotland*

As in Wales, the approach to encouraging cluster growth in biotechnology involves the public funding bodies more centrally than in the market-driven clusters of Cambridge and Oxford or even the agglomeration of biotechnology firms in Surrey. However, while Wales has some fifteen biotechnology firms in mini-agglomerations in Cardiff and Swansea, Scotland has over fifty biotechnology firms. The biggest geographical concentration is in Glasgow but there is strong science and spin-out firms also in Dundee and Edinburgh as well as near Aberdeen. The sector is thus seen as occupying a "biotechnology triangle" between Dundee, Edinburgh and Glasgow at its heart.

The role of the public sector has been important in Scottish biotechnology in three ways. First, as elsewhere, the finance for basic scientific research in the universities is mainly provided by U.K. Research Councils and, to a lesser extent and influenced by the measures of scientific legitimacy conferred by the high public ranking of biosciences schools, university hospitals and the like, this also attracts private sector funding from big pharma or charitable trusts. Second, the sector has benefited from the adoption of a cluster strategy by Scottish Enterprise, the development agency for Scotland. Scottish Enterprise commissioned Michael Porter's consultancy, *Monitor*, to conduct a scoping exercise and provide intensive, back-up training for developing four pilot clusters, one of which was biotechnology. This has now begun in earnest and the methodology by means of which cluster building is taking place is established (see Figure 1). It is noteworthy that this methodology, the whole cost to Scottish Enterprise for which was $2 million, is unlike what might be termed a more normal planning and programming approach.

Instead, it places great emphasis on the processes of scoping, picturing and resourcing a "vision" of the cluster. Then, armed with the cluster vision, stakeholders and leaders willing to




(Stakeholders: industry, academia, education, research, government and other institutions)
*Source:* Scottish Enterprise.

Figure 1. The Scottish enterprise cluster approach in biotechnology.

show strong commitment, bring together key actors and those engaged in interactive learning are assembled. Only then, at the third stage, does data gathering, benchmarking and scenario building begin. This leads to action planning based on consensus and concrete agreements followed by implementation guided by cluster visions, leaders, expenditures and evaluation. This is a market-influenced model of public enterprise based on the ideas of "picture, manage and monitor", rather than "survey, analysis and plan".

The third way in which public intervention has a generic impact on biotechnology in Scotland flows from the consensus agreement on the cluster strategy at a Scotland-wide level, and the collaboration by governance bodies to pool funding to assist in the process of supporting, in this case, the biotechnology sector (see Scottish Office, 1999). Thus, Scottish Enterprise, the Scotland Office and the Scottish Higher Education Funding Council created a fund of some £11 million to enable all clusters to develop by innovative means. As an example, funding is being made available to "buy-out" or "free-up" the time of bioscientists and biotechnologists to concentrate on research and commercialisation activities instead of teaching and administration (known as the 'Proof of Concept' fund). This is administered with local knowledge and sensitivity through the decentralised Scottish Local Enterprise Companies with whom candidate academics discuss their prospects for receiving funding.

Despite this excellent public support, the existence of biotechnology as one of the cluster-building projects is testimony to the fact that, although having considerable potential, the biotechnology sector does not yet constitute a cluster in the way that Cambridge, Massachusetts or Cambridge, England (at a smaller scale) does. This is partly because spin out activity is relatively recent, partly also due to the limitations of the local, private venture capital industry and the relatively late recognition by public bodies of the role they, together and in partnership, can make to assisting the commercialisation of often excellent basic science. Scotland is globally known as the home of the first transgenic animal, Dolly the sheep, developed at the Roslin Institute near Aberdeen. Other specialities include drug discovery, evaluation and clinical trial management in cancer research, cystic fibrosis, Alzheimer's and Parkinson's diseases. Scottish biotechnology also has a significant presence in agro-biotech, with animal health and breeding, veterinary medicine, crop yields and pest control. Firms deploying environmental biotechnologies are also present. In

all, Scottish Enterprise claim a "cluster" of some 180 core and supply or service firms engaged to some degree in the "cluster". In truth, the core is some 40–50 firms and they are quite geographically dispersed and focused mainly on their scientific home bases.

The industry in Scotland is made up broadly as follows (Table VII). It is clear that biopharmaceuticals is the strong, core part of the industry in Scotland, with a substantial number of firms in therapeutic product development, fewer in diagnostics, research and clinical trials (many of the contract R&D entries are universities, some with firms attached, others not). There is also a reasonably well-endowed supplies (reagents, chemicals etc.) and support services (legal, consultancy etc.) infrastructure. Hence, as a whole, Scotland has a robust basis for future growth in biotechnology, but it may lack, at present, the interactive capacities and sophisticated support arrangements found more extensively in Cambridge and Oxford. Having said that, it is undoubtedly closer in type to those university-based clusters and quite unlike the rather amorphous agglomeration found in Surrey. In Dundee, there are a number of highly rated bioscience departments in the university, and a new Wellcome Trust-funded biotechnology institute. Cyclacel, which will be described below, and Shield Diagnostics, a manufacturer of immunoassays in cardiovascular diseases, are spin-outs, the first located on the nearby innovation park of Dundee University, the second having graduated beyond it as it has grown in size. The Ninewells Hospital Medical School has some 250 bioscience researchers to contribute to the total of 1,000 life scientists in Dundee. Of these 170 are in the Wellcome Trust Institute (which opened in 1997) rising eventually to 240.

TABLE VII
Composition of biotechnology sector in Scotland

| Activity | Number of firms (core activity) |
|---|---|
| Biopharmaceutical therapeutics | 24 |
| Biopharmaceutical diagnostics | 18 |
| Biopharmaceutical clinical trials | 10 |
| Biopharmaceutical contract R&D | 14 |
| Bioprocessing | 17 |
| Environmental bioremediation | 3 |
| Environmental diagnostics | 7 |
| Environmental waste treatment | 5 |
| Ag-Food therapeutics | 1 |
| Ag-Food plant breeding | 2 |
| Ag-Food diagnostics | 4 |
| Ag-Food contract R&D | 2 |
| Supplies | 23 |
| Support services | 26 |

*Source:* Biotechnology Scotland Source Book, 1999.

Dundee thus has the science base for possible future cluster development but as yet lacks critical mass of firms. Cyclacel is a contract R&D spin-out specialised in drug discovery for cancer genomics, the key connection is with the Ninewells Medical School, headed by David Lane (co-owner of Cyclacel) who discovered the p53 anti-cancer gene. Venture capital of £2.5 million was accessed from London-based Merlin Ventures, headed by biotechnologist Chris Evans, who founded Chiroscience, one of the U.K.'s leading biotechnology firms. Chiroscience, it will be recalled, recently merged with the U.K.'s first biotechnology firm Celltech, subsequently acquirers of pharmaceutical firm, Medeva.

Cyclacel contracts-in research from American head-quartered Quintiles, one of the world's leading biotechnology contract research firms from Boston, this subsidiary based in Edinburgh. Quintiles entered Scotland by acquiring Innovex, an upstream biosciences spin-out from academia. Another firm, now located in Perth, called Quantase is present near Dundee because of Shield Diagnostics based on the Technology Park at Dundee. Quantase conducts neonatal screening and was acquired by Shield in 1994. Shield specialises in cardiovascular neonatal diagnostics. In September 1997, however, Quantase was subject to a management buy-out, employs eight people, of whom three are research scientists and has won government innovation awards to support development of its leading product. Expansion has been funded by venture capital from U.K. firm 3i and bank loans. Quantase, like Cyclacel and Quintiles, find the environment in Perth highly suitable for their business activities. Linkages between firms are regular and established even though geographical co-location is not considered a pre-requisite. Communication links between Dundee and Edinburgh, particularly, are extremely easy and swift. Moreover, Glasgow is well-linked to both by high grade transportation links.

This small snapshot of biotechnology in

Scotland shows that the sector has the characteristics of close inter-firm interaction often found in clusters, and taking the form of network linkages. In Scotland as a whole, there are largely adequate business infrastructures to sustain a successful biotechnology sector. Private capital for biotechnology investment is not abundant in Scotland, but this is partly compensated by the presence of public sector support in this well-networked, latent cluster.

## 6. Concluding remarks

This paper began with a commentary on how dependent big pharma has become upon significantly smaller technology-driven start-up and spin-off firms. This was demonstrated in detailed analyses of biotechnologically-derived therapeutic treatments manufactured, marketed or distributed by the multinational pharmaceutical companies. Whichever way diverse data sources are analysed, big pharma is overwhelmingly dependent for drug-origination upon independent, lesser-scale, biotechnology firms. Of course, the latter are dependent on the former to at least as great an extent for the large cash-investments required to test and trial potential products over lengthy time periods and at high risk. Big pharma is cash-rich enough to continue this asymmetrical power game for as long as biotechnology firms fail to make the scale breakthrough to become fully integrated pharmaceutical companies or FIPCOs. This kind of relationship of double, but asymmetrical, dependence is probably unique in the business world, though it has a resonance with the way the IT industry operated in its earlier days, when electronics multinationals quarried Silicon Valley for technologically sophisticated start-ups. By the end of the millennium, of course, some of the bright start-ups of the 1970s and 1980s had themselves outgrown or displaced the larger predators, as the histories of Microsoft and Intel exemplify. The paper is unable to say that a comparable process of independent, technology-focused firm growth from start-up to market leader will happen in biotechnology as it has, to a growing extent, in IT. This is not ruled out, but what can be stated with confidence is that the model of venture capital-driven, start-up and spin-out growth, usually in business clusters, has now spread from the U.S. to Europe, particularly in the U.K., and that, if anything, big pharma shows less signs of being at the research cutting-edge of biotechnology in the era of the human genome than it did in the days of monoclonal antibodies and recombitant DNA. Moreover, a first case of biotechnology acquiring pharmaceuticals occurred with the Chiroscience-Celltech purchase of Medeva in November 1999 in the U.K. There has also been some equalisation of the technological lead in product commercialisation between the U.S. and Europe as the climate for academic entrepreneurship has improved in the latter.

There are even some signs in the U.S. that the biotechnology firm formation rate has declined with merger and acquisition practices among biotechnology specialist firms. This may signify a new stage in the industry's slower evolution towards a less bifurcated structure than hitherto. Peak years for new firms in Massachusetts, for example, were 1991–1993, with annual start-up rates of 15, 21 and 15. Between 1996 and 1998 seven Massachusetts firms merged or were acquired by others (Massachusetts Biotechnology Council, 1998). Alternatively, it may be a lull before the storm of potential new firm formation associated with functional genomics as gene-sequencing, bioinformatics and a host of other commercial applications of human genome science are explored. More of this kind of activity is likely to occur in the U.K. as well as elsewhere in Europe, than happened in the first wave of biotechnology application growth in the 1980s when key discoveries remained unpatented in U.K. laboratories, leaving U.S. technologists a clear field for early adoption and application. Despite its European lead in biotechnology product potential the U.K. is, in 1999, as dependent on the U.S. for biotechnological therapeutic products, marketed and distributed by big pharma in the U.K., as Germany. However, U.K. independent biotechnology firms dominate the European pipeline for future biopharmaceutical products, and many of these involve alliances with U.K. pharmaceutical firms. Cantab Pharmaceutical's vaccine partnerships with Glaxo and SKB, Powderject's with Glaxo, and Peptide Therapeutics with SKB are illustrative of this tendency. But U.K. alliances with non-U.K. pharma, like Cambridge Antibody Technology's

with Eli Lilly, Chiroscience's with Schering-Plough, Bristol Myers Squibb and AstraZeneca, and Scotia Holdings with Boehringer Ingelheim are noteworthy and show that the levelling-up between U.S. and European entrepreneurial firms is now a reality in prospect rather than mere hype.

The final inference to be drawn from this analysis of global-local power dependencies and asymmetries is two-pronged. First, "strength-in-numbers" characterises the practices of the small firm ecosystem defining the originators of potential biopharmaceutical products and platform technologies. The cluster is the definitive organizational mode of the creative community of firms that risk oblivion to pursue discovery and commercialisation. Investment is tight, so situations that can lower transaction costs or remove them *via* trustful exchange, reputational trading and collective learning in localised knowledge networks is of key importance. And the prospects of long-term profit continue to attract the complementary business, legal and financial services companies into the cluster alongside the research laboratories, incubators and start-up firms. This is an "extended campus" milieu rather than the "extended workbench" metaphor applied to clusters in more traditional industries such as those of northern and central Italy. But this also highlights the second feature of the "triple-helix" relationship between industry, university and government (Etkowitz and Leydesdorff, 1997), which is that big pharma and the entrepreneurial biotechnology firms are inordinately dependent also upon the public purse. For example, some $770 million of public research funding flows through the Boston biotechnology community per year, and it is at least $1 billion each in San Francisco and San Diego. The U.S. biotechnology funding agencies had at their disposal $20 billion of public money in 1999, more than twice as much as the business R&D budget of $9 billion. This is by no means only an innovation process involving venture capital, management support and start-ups to transfer research results from laboratory to market. It is fundamentally fuelled by public research budgets. Estimates of the value of the market at $70 billion in 2000 give an indication of the public: market value ratio. Keep in mind also that U.K. government annual expenditure on bioscience research is some £1 billion and Germany's a further $1 billion if the large public element in biotechnology venture capital is included, and we see something of the scale of modern public investment in this industry of the future (Cooke, 1999; DTI, 1999a). In conclusion, the globalisation of bioscience and its commercialisation in biotechnology is a study in variable geometry between multinationals and entrepreneurial start-ups, competition and collaboration, public subsidy and private profitability, or as some might also say, the devil and the deep blue sea.

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